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THE MEDICAL CLINICS of NORTH AMERICA

PHILADELPHIA NUMBER

SYMPOSIUM ON RECENT ADVANCES IN GYNECOLOGY AND OBSTETRICS

FOREWORD

IN arranging with various colleagues in Philadelphia for the preparation of this symposium on obstetrics and gynecology, we have chosen to include a range of subjects which, while not "new" in the popular sense of the word, are of substantial value because of their basic importance. Nevertheless, it is equally true that one cannot review any subject in these fields without presenting recent advances based on changing concepts and conditions, and thereby provoking controversy in some instances.

A goodly number of the contributors are associated with the staff of the Department of Obstetrics and Gynecology at the Jefferson Medical College and Hospital, or with other departments of that institution. It has not been our intention to restrict the symposium to one teaching group, however, and for that reason we have had the welcome cooperation of distinguished staff members from other medical schools and hospitals, notably from the graduate and undergraduate schools of the University of Pennsylvania, Temple University, Woman's Medical College, and from several hospitals associated in some capacity with the medical schools mentioned, viz. Episcopal, Philadelphia General, Pennsylvania and Jewish. Hence, we feel that the presentations of this symposium represent a liberal index of the ideas and accomplishments of the Philadelphia group in today's obstetrics and gynecology.

It seems a bit superfluous to comment upon each subject presented in the following pages. Suffice to say that, in reviewing them, a logical sequence is observed. The physiology and endocrinology of menstruation is followed by the therapy of functional disorders, and the problem of

fertility and infertility. Next come the factors involved in the prompt recognition of early pelvic malignancy, so necessary if management is to be adequate. Certain important gynecologic problems are then considered with a view to philosophic as well as specific correction. Turning to the realm of obstetrics, nutrition and significant prenatal problems precede discussions of x-ray pelvimetry, the toxemic state, analgesia and the rediscovered postpartum intimacy of baby and mother.

We cannot help but feel that the information contained is of practical value, presented with clarity and understanding by able contributors to whom our thanks are due. It is our aim that this Philadelphia number of the *Medical Clinics of North America* will not only prove worthy of the time and effort expended by the authors, but that it will be of distinct value to their readers.

LEWIS C SCHEFFER, M.D., Sc.D. (HON.)

PRESENT CONCEPTS OF THE PHYSIOLOGY AND ENDOCRINOLOGY OF MENSTRUATION

JACOB HOFFMAN, M.D.*

PERIODIC bleeding from the uterus is a normal concomitant of sexual maturity in the human and subhuman primate 'Menses,' "menstrual flow," "catamenia" and "menstruation" are among the terms long used to describe this physiologic bleeding. Since its appearance coincides roughly with the childbearing period, it has traditionally been the symbol of sexual maturity and potential fertility. The studies of Hitschmann and Adler,¹ R. Meyer² and Schroeder,³ who correlated events in the ovary and uterine mucosa, seemed to bear out this impression. Follicular maturation, ovulation and corpus luteum formation, they found, coincides with growth of the endometrium and its conversion to secretory activity, preparatory to nidation. Regression of the corpus luteum for want of a fertilized ovum, is followed by menstruation, a degenerative process involving dismantling of the pregravid endometrium. Their studies thus established menstruation as the outward manifestation of a frustrated effort to achieve fertility.

Conflict as to the correct application of the term 'menstruation' first arose with reports that periodic bleeding, clinically indistinguishable from that which accompanies the ovulatory cycle, may punctuate in complete ovarian cycles in which follicular maturation fails to culminate in ovulation and corpus luteum formation. Two schools of thought now prevail. One maintains that the bleeding is essentially the same in both the ovulatory and anovulatory cycle and the term 'menstruation' should therefore apply to both. The other limits the term to bleeding which follows ovulation and corpus luteum formation and accompanies disintegration of a pregravid endometrium. For periodic bleeding in the absence of ovulation, the terms 'anovulatory menstruation' and 'pseudo-menstruation' have been coined. I favor the latter view, for while there are some points of similarity between the two types of bleeding, their differences, not only in the events that precede them but in the details of the bleeding process, are sufficiently fundamental and striking to warrant their being treated as distinct entities.

In seeking the answer to the riddle of menstruation, investigators have tried to determine what events precede it and the part they play, and to

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**DIFFERENCES BETWEEN OVULATORY AND
ANOVULATORY MENSTRUATION**

| Ovulatory Menstruation | Anovulatory Menstruation |
|---|---|
| Preceded by ovulation and corpus luteum formation | Preceded by follicular maturation without ovulation or corpus luteum formation |
| Precipitated by corpus luteum regression with consequent estrogen and progesterone withdrawal | Precipitated by abrupt drop in estrogen level |
| Accompanies disintegration of a secretory type of endometrium | Accompanies disintegration of a proliferative type of endometrium |
| Preceded by growth of coiled arteries to just under surface, highly coiled, thick walls | Preceded by growth of coiled arteries about halfway through the endometrium, limited coiling, thinner walls |
| Regression of mucosa extensive | Regression of mucosa less extensive |
| Increased coiling during regression marked | Increased coiling during regression much less marked and appears later |
| Stasis and vasodilatation intense | Stasis less intense and vasodilatation often absent |
| Phase of vasoconstriction more prolonged | Phase of vasoconstriction shorter |
| Blood loss greater, larger proportion of hemorrhages from arterioles and capillaries | Blood loss less, larger proportion of hemorrhages from veins |
| Disintegration diffuse and explosive, tissue loss extensive, large fragments | Disintegration focal and prolonged, tissue loss limited, small fragments |
| Destruction involves capillaries, arterioles and part of arteries | Destruction involves capillaries and part of arterioles |
| Endometrial debris contains "menstrual toxin" | Endometrial debris contains less "menstrual toxin" |
| Subjective molimina often present. | Subjective molimina mild or absent |
| Sudden marked change in urinary metabolites of estrogen indicating increased oxidative inactivation | No such change |

identify the immediate cause of the bleeding. In their first quest they have been fairly successful, but identification of the immediate cause of

the bleeding has proved a more stubborn problem which still awaits final solution.

EVENTS LEADING TO MENSTRUATION

Menstrual bleeding is the end point in a complex chain of events involving the *anterior pituitary gland, ovary and uterus*.

The *anterior pituitary gland*, so-called 'motor of ovarian function,' elaborates 'gonadotrophic' hormones specifically concerned with ovarian function. Their number and relationship to other anterior pituitary products, the precise manner in which they act on the ovary, are questions which await complete clarification. However, clinical and experimental evidence, which has assumed considerable proportions during the last few decades, would seem to justify the following assumptions. A *follicle stimulating factor* from the anterior hypophysis acts on a young follicle in the ovary, causing it to enlarge and mature. The simultaneous action of a minute amount of a second factor, so-called '*luteinizing principle*', is apparently needed to enable the developing follicle to secrete its specific estrogenic hormone. A somewhat larger admixture of this luteinizing factor, acting with the follicle stimulator at the height of follicular maturity, induces rupture and extrusion of the ovum. Increasingly larger amounts of luteinizer, acting on the collapsed follicle, transform it into a corpus luteum. Whether the luteinizer or some other anterior pituitary factor, possibly '*luteotrophin*,' sustains the function of the formed corpora lutea, is not certain. Whatever the identity of this sustaining factor, its withdrawal is apparently responsible for the corpus luteum regression which occurs in the absence of conception and terminates the infertile ovarian cycle.

In the *ovary*, a follicle matures and secretes estrogenic hormone, ruptures approximately at the midcycle and, on conversion to a corpus luteum, secretes estrogen plus a specific pregestational principle, progesterone. It is through the action of these two hormones that the ovary elicits in the uterine mucosa the characteristic morphologic changes that invariably precede menstrual bleeding in the normal ovulatory cycle. Regression of the corpus luteum and withdrawal of its hormones coincides with the endometrial changes which are premonitory of and eventually culminate in menstruation.

Before proceeding to a consideration of the uterus, whose response to these and possibly other stimuli determines the onset, amount and duration of menstrual bleeding, the part played by *ovarian hormone withdrawal* in this phenomenon will be considered. Evidence that the onset of the flow coincides with corpus luteum regression was largely responsible for the assumption that menstruation is precipitated by loss of some sub-

stance or substances secreted by this structure. This belief was strengthened by the observation that excision of a functioning corpus luteum is soon followed by uterine bleeding. The identity of the hormone whose withdrawal leads to menstrual bleeding has been the subject of much controversy. Since the human corpus luteum secretes both estrogen and progesterone, the bleeding which follows its regression or destruction may conceivably be due to withdrawal of either or both these hormones.

Estragen withdrawal as the cause of menstrual bleeding was first suggested by the observation that bleeding, clinically resembling menstruation, may follow bilateral oophorectomy performed at a time when neither ovary contains a functioning corpus luteum. The occurrence of periodic menstruation-like bleeding in man and monkey, without preceding ovulation and corpus luteum formation, also seemed to point in this direction. Since such bleeding occurs from a mucosa subjected only to the action of estrogen, it was argued that all periodic uterine bleeding, whether from a proliferative or secretory type of endometrium, may be accounted for on the basis of estrogen withdrawal. Support for this view was provided by reports that bleeding, which follows ovariotomy performed during the follicular phase, can be materially reduced or, if not yet started, can be prevented by administering estrogen, and further, that bleeding can be induced in the castrate monkey or woman by giving a series of estrogen injections and then withholding treatment. To insure the latter effect, the subject must have achieved a certain degree of maturity, and minimum requirements as to daily dosage and length of treatment must be fulfilled. Moreover, withdrawal of the hormone must be abrupt. Complete withdrawal is not essential provided the hormone level is permitted to fall below a certain crucial point, the so-called bleeding threshold.

This theory has been questioned on the ground that normal menstruation is associated with large amounts of estrogen in the body fluids, and further, that during protracted estrogen administration in the macaque, one or more bleeding episodes occur despite a constant supply of estrogen. In explanation, protagonists of the estrogen withdrawal theory have postulated the existence of some excretory mechanism, which periodically increases estrogen destruction or elimination. Zuckerman⁴ suggested that cyclic variations in the activity of the adrenal cortex may, by reason of its effect on water metabolism, cause a cyclic rise and fall in the threshold for estrogen stimulation. A rise and fall in estrogen production due to the interplay between the anterior pituitary and ovary has also been considered. Both possibilities have been eliminated by the observation that neither hypophysectomy⁵ nor adrenalectomy⁶ prevents the

periodic bleeding which occurs in spayed monkeys receiving daily injections of estrogen

An explanation of bleeding despite a constant estrogen supply may possibly be found in the response of the endometrium. There is evidence⁷ that under chronic estrogen stimulation the mucosa thickens until it reaches a point where the original dose is inadequate to maintain it, whereupon disintegration and bleeding occurs. It has also been noted⁸ that such treatment may evoke rapid proliferation at first but eventually, due possibly to exhaustion, the mucosa ceases to grow despite continued stimulation. Still another explanation for bleeding during estrogen administration may be found in the response of the vascular apparatus, which may become overgrown and disorganized and consequently prone to bleeding by rhexis or diapedesis the condition being analogous to that encountered in irregular bleeding associated with endometrial hyperplasia, an entity generally attributed to chronic estrogen stimulation. If any of these explanations may be considered acceptable, bleeding during protracted estrogen administration loses its force as an argument against estrogen withdrawal as the cause of menstruation.

This theory has also been questioned on the ground that bleeding may fail to occur despite a drop in the estrogen level. Thus Fluhmann⁹ observed that in some women a recurring rise and fall in the estrogen level of their body fluids is associated with amenorrhea. A possible answer to this objection may be found in the mucosa, which may fail to react to the estrogen present with a degree of growth sufficient to insure bleeding when the estrogen supply is reduced. Alternatively, the growth response may be adequate but the drop in estrogen may not be sufficiently steep or abrupt to result in bleeding.

The long latent period which may intervene between cessation of estrogen administration and bleeding has been offered as proof that some factor other than estrogen withdrawal is the immediate cause. Engle and Crafts¹⁰ found that bleeding may begin as late as thirty to seventy days after a single injection of estrogen in castrate monkeys. In the absence of more definite information concerning the absorption, utilization and elimination of estrogens, and in view of the possibility that products of other glands, particularly the adrenal cortex, which are closely related chemically to the ovarian hormones, may combine with the administered hormone to maintain the mucosa, this evidence cannot be accepted as conclusive proof against the estrogen withdrawal theory.

On the whole, though the question cannot be considered completely resolved, estrogen withdrawal seems to offer a reasonable explanation for bleeding from an estrogen stimulated mucosa. It does not neces-

sarily follow, however, that it can also account for bleeding from a pre-gravid mucosa. The part played by *progesterone withdrawal* in such bleeding has been difficult to define because the necessity for preliminary preparation by estrogen, without which progesterone cannot act, tends to obscure the picture.

In an attempt to solve this problem, Zuckerman¹¹ induced cyclic bleeding at twenty-eight day intervals in castrate monkeys by administering increasing doses of estrogen up to 3000 I U for fourteen days, followed by a threshold dose of 100 I U daily for fourteen days. This monthly rhythm was not significantly altered when progesterone was given on the first ten to twelve days of the period during which the smaller dose of estrogen was used. He concluded that a wave of estrogenic stimulation is the basic mechanism of the menstrual cycle. That progesterone plays a minor role or none at all would also seem to follow from his observation. Were this true, however, the converse should follow, namely that estrogen alone can postpone bleeding from such a mucosa while progesterone is of little or no avail for this purpose. This, however, is not the case. There is ample evidence that progesterone, in adequate amounts, can delay bleeding for long periods of time, whether the mucosa has previously been stimulated by estrogen alone or by estrogen plus progesterone.¹² Estrogen, on the other hand, can postpone bleeding from an estrogen-stimulated mucosa but quickly loses its efficiency in this respect if a progesterone effect is allowed to intervene.¹³ Large doses of estrogen administered during the luteal phase of the cycle fail to delay the flow. In the ovulatory cycle in the human, bleeding occurs despite the presence of large amounts of estrogen in the body fluids, uterine mucosa and menstrual blood.¹⁴ Zondek's simplified treatment of amenorrhea,¹⁵ which calls for the injection of progesterone in cases where endogenous estrogen is present, depends on the fact that the estrogen-prepared mucosa, once subjected to progesterone influence, cannot be maintained by estrogen. In monkeys receiving chronic estrogen treatment, a short series or even a single injection of progesterone is followed by bleeding despite continued estrogen administration.¹⁶ Only by using very large doses of estrogen is it possible to postpone bleeding from a progesterone-stimulated mucosa.¹³

It would seem that estrogen, which is growth-promoting, and progesterone, which induces secretory activity, compete physiologically for mastery of the endometrial cells. As pointed out by Loeb,¹⁷ there is an antagonism between mitotic cell proliferation and function. "Growth inhibits those alterations in the cell which tend to initiate certain functional activities like secretion, and progressive differentiation is unfavorable to the development of those changes on which mitotic division

depends." The point at which one or the other hormone gains mastery, and the nature of the change that determines when one or the other shall be dominant, still remains to be answered. Hisaw¹² has suggested, on the basis of studies in the marmoset, that the particular effect of progesterone which robs estrogen of its power to maintain the mucosa and prevent bleeding, occurs much earlier than the glandular changes and probably involves the stroma and blood vessels. In this connection, Watson and McHenry¹³ observed that the bleeding which follows injection of estrogen followed by progesterone in the castrate monkey is associated with necrosis limited to the epithelium of those glands fully activated by progesterone and the stroma surrounding them.

On the whole, it seems likely, from the available evidence, that bleeding from a pregravid mucosa is due to withdrawal of progesterone and, to a lesser extent, of estrogen. The relative importance of each probably varies according to the completeness of the pregravid transformation, which in turn depends on the extent of the endometrial structure built up by estrogen, the amount of progesterone available, the length of time it is permitted to act, and the reactivity of the mucosa to the two hormones. Estrogen probably loses its ability to prevent endometrial bleeding when the area over which progesterone has gained supremacy is so extensive that its dissolution, in the event of progesterone withdrawal, brings in its wake a destruction of the supporting stroma and blood vessels sufficiently far reaching to result in outwardly visible bleeding.

IMMEDIATE CAUSE OF MENSTRUAL BLEEDING

The uterine mucosa or *endometrium*, which is the source of the menstrual flow, would seem to be the logical place to look for a clue to the immediate cause of menstrual bleeding. The modifications which it undergoes in the course of the cycle involve its chief components, glands, stroma and blood vessels. Knowledge of the complex interaction between these elements is indispensable to an understanding of the menstrual process. The nature and significance of the cyclic changes in the glands and stroma are well understood, thanks to the work of Hitschmann and Adler,¹ R. Meyer,² Schroeder³ and others who have since confirmed their findings. The structure and cyclic behavior of the blood vessels have only recently received the attention they deserve if menstruation, which is essentially a vascular phenomenon, is to be understood.

The endometrium begins abruptly at the internal os and lines the entire uterine cavity. Two layers are distinguishable a *basal* or foundation layer and a superficial *functional* layer, which alone shows cyclic changes and is involved in the degenerative process that terminates each cycle. A cellular connective tissue harbors the tubular glands, each of

which is supported by a delicate basement membrane and lined by epithelial cells that also cover the surface of the mucosa. The glands have their roots in the basal layer and extend perpendicularly, their mouths opening into the uterine cavity.

Our knowledge of the *endometrial vasculature* is based on studies in the human¹⁹⁻²³ and subhuman primate,²⁴⁻²⁷ particularly the macaque. Histologic examination of endometrial curettings, studies of extirpated uteri injected with India ink, and observation of intraocular endometrial transplants in the macaque are the chief sources of information regarding the general histological characteristics of the endometrial blood vessels and their relationship to the endometrial glands and stroma through the various phases of the menstrual cycle. None of these methods is free from

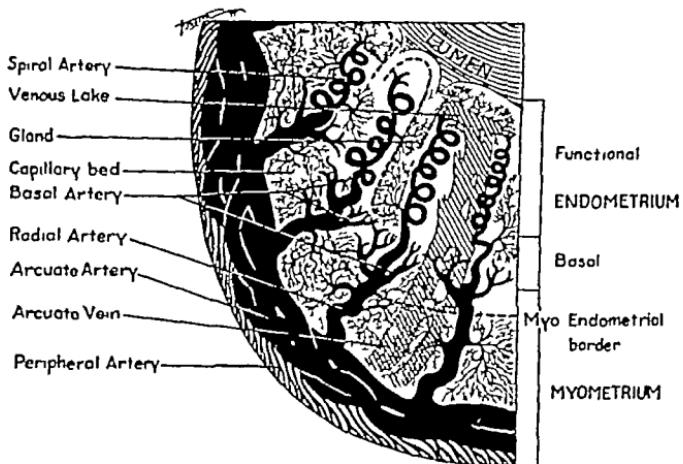


Fig 177.—Schematic representation of the specialized vascular elements in the human uterus (Reynolds in J A M A , Vol 135)

objection, but despite the disadvantages inherent in each, they have yielded information sufficiently consistent to provide a fairly definite picture of the vascular supply of the endometrium (Fig 177).

The primate uterus, which differs from that of other mammals in its hemorrhagic type of desquamation, is endowed with a vascular tree in certain respects unlike that of other species. The external layer of the myometrium is traversed by many large, so-called "arcuate" arteries, which run in a direction concentric with the peritoneal surface and form a complete vascular ring around the uterus. They give rise, at right angles, to branches which penetrate the muscle layer in the direction of the endometrium. These branches or "radial" arteries give rise in turn, at a point near the myoendometrial border, to two distinct types of artery. The smaller of these is relatively straight, devoid of elastic apparatus but

possesses a well developed muscular coat. Running parallel to the myometrium, it is limited in its extent to the basal layer of the endometrium, from which fact it derives its name *basal artery*. The second type is larger, tightly coiled and rich in elastic fibrils. It enters the functional layer, running perpendicularly to the myometrium and is accompanied by encircling strands of connective tissue more or less distinct from the surrounding stroma. The terms coiled or spiral are usually applied because of its tortuous configuration. In microscopic section, the spiral artery appears as an arterial field, defined as a limited area filled with numerous transverse and oblique sections of the artery surrounded by a dense stroma.²⁴ These fields are now conceded to represent a single coiled artery and not, as was earlier thought a bundle of arteries.

The *basal arteries* take no part in the changes occurring during the menstrual cycle. Their status remains unchanged whatever the stage of the cycle or the parity of the individual.²⁵ After leaving the radial arteries, they divide dichotomically a few times, entering into the formation of the capillary network of the basal layer, which envelopes the basal ends of the glands. Anastomosis of the capillary layer of the basalis with that of the myometrium has been observed.²⁶

The *spiral arteries*, most distinctive feature of the primate endometrium, form tightly twisted columns that radiate from the myoendometrial border. In their course through the endometrium, they give off but few branches which divide dichotomically a few times and then enter into an abundant capillary network arranged chiefly around the glands, the axis of the long meshes being parallel with that of the glands. At a variable distance from the surface depending on the phase of the cycle (see below), the spiral arteries divide abruptly, usually into three or four branches or terminal arterioles. The latter divide dichotomically, some entering into an abundant capillary network parallel with the surface and enveloping the glands. As described by Dalgaard,²⁷ the arterioles that arise from each artery run along each gland and are connected by small capillaries forming a blood capillary cylinder outside the gland. The blood cylinders of the various glands are connected by anastomosing capillaries.

The *venous system* of the endometrium, as described for the macaque by Daron,²⁸ is composed of many small veins which run parallel to each other in a centrifugal fashion from the uterine lumen, without uniting to form larger trunks towards the basalis. He observed numerous anastomoses at acute angles between parallel veins. At the site of certain anastomoses in the middle third of the endometrium, there appear greatly dilated veins which he describes as venous lakes. According to Markee,²⁹ the functionalis and basalis, though fed by independent arterial

systems, have a common venous drainage. In human uterus, Bartelmez²⁰ found that drainage from the endometrium is through venules, which are chiefly radiate but form numerous anastomoses that may increase in size to become sinuses. Some of the venules pass without anastomosis from the superficial endometrial veins to the deep ones. Schlegel²¹ and Dalgaard²² have recently emphasized the occurrence of arteriovenous anastomoses in the human endometrium, that is, direct contacts between arterioles and venules, by-passing the capillaries. According to Schlegel, the venous efflux begins in two ways as venous capillaries entering into venules, and as venous lakes drained by venules. In addition to numerous capillaries, arterioles enter directly into these lakes, which he interprets as venules that have dilated because of high pressure resulting from their direct contact with arterioles. As described by Dalgaard, the venous system consists of a superficial venous plexus, a single broad venous trunk running just under the surface and interposed between the capillaries and venous lakes, on one side, and collecting veins on the other. This plexus may be divided roughly into a superficial part parallel to the surface, a middle zone with veins running in all directions, and an inner zone in which the main direction is radial. Some of the veins drain into collecting veins, others connect directly with the veins in the basalis. The collecting veins, which have not been observed in the macaque, take the form of large trees running radially.

In the basal layer, the venous net is simpler than in the functionalis. The veins are mostly radial, being often merely a continuation of the radial part of the network in the functional layer. They may either enter the collecting veins or continue through the boundary layer, ending as myometrial veins (See Fig. 178).

Cyclic Endometrial Changes—The endometrial cycle consists of an *anabolic* and a *catabolic phase*. The former involves a progressive growth and preparation of the mucosa for nidation. The catabolic phase, clinically manifested in menstrual bleeding, involves breakdown and dismantling of the fully developed mucosa. The changes are continuous so that there is no clear-cut point at which one phase ends and the next begins, but it is customary, for descriptive purposes, to divide the cycle into an early and late proliferative phase, occupying approximately the first half of the cycle, and an early and late secretory phase, occupying the latter half, except for the last few days when regressive changes initiate the catabolic phase.

ANABOLIC PHASE—In the *early proliferative phase*, which coincides with the follicular phase in the ovary, the endometrium appears as a thin, denuded membrane about 1 mm thick. It is composed of a dense, cellular, poorly vascularized, spindle-celled stroma, which harbors the

basal portions of the endometrial glands. The latter consist of tubular stumps with narrow lumina and show only slight branching. Widely separated, they run either perpendicularly, obliquely or parallel to the surface. Few or no mitotic figures are observed. The epithelial cells lining the glands contain elongated, oval shaped, darkly staining, basally situated nuclei. The protoplasmic zone of the glandular epithelium is

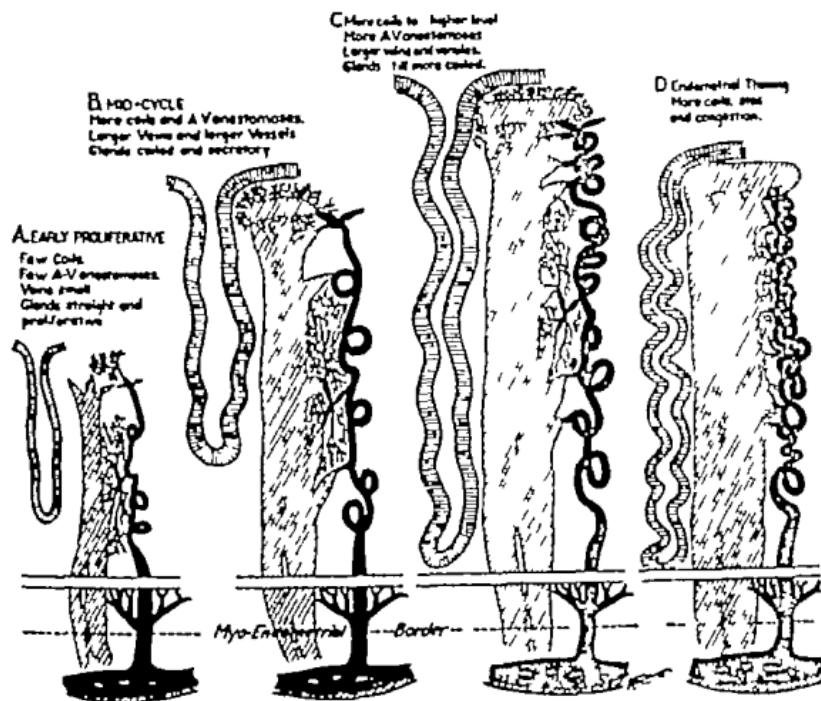


Fig. 178.—Schematic representation of the development throughout the menstrual cycle of an endometrial spiral or coiled arteriole, collecting veins, subepithelial venous lakes and arteriovenous anastomoses described by Schlegel. The basal endometrium which remains relatively unaffected is indicated below the break in continuity of the endometrium. Based on descriptive data of Schlegel (1915-46)²¹ Markee (1940)²² and Daron (1930)²³ (Reynolds in J A M A Vol 135)

sharply demarcated and the lumina of the glands are empty. Veins and arteries project freely into the uterine cavity and, like the stumps of the glands, are enveloped by a dense sheath of reticulum. Re-epithelialization begins about the third day after the onset of the preceding flow and is complete by the end of the second week.³ It is apparently accomplished by radial migration of the epithelial cells lining the wide mouthed glandular stumps. Capillaries pass from the stumps of the spiral arteries to the superficial reorganizing zone, which rapidly increases in thickness. Some lengthening of the arteries and veins occurs at this time.

In the *late proliferative phase* (Fig. 179), mitotic activity is marked and the mucosa increases in thickness to about 3 mm. Growing longer and wider, the glands follow a course perpendicular to the surface. Towards the end of this phase, they assume mild serpentine formations, the cells lining them are higher and their oval nuclei are basally or centrally situated. The stroma acquires a looser texture and becomes more and more vascularized, due to growth of capillaries and gradual extension of the spiral arteries. At the height of this phase, according to most ob-



Fig. 179.—Proliferative type of endometrium. Microphotograph of tissue obtained twelve days postmenstruum (Hoffman: Female Endocrinology)

servers, the spiral arteries are limited to the deep third or at most the deep half of the endometrium, due to the more rapid growth of the surrounding tissue.^{25 27} The increasing richness of the capillary and arterial supply during this phase is associated with the appearance of venous lakes at the site of arteriovenous anastomoses in the superficial and deeper zones of the functionalis.^{21 23}

In the *early secretory phase*, which follows ovulation and coincides with the corpus luteum phase in the ovary, the mucosa thickens, the glands become more tortuous and the stroma better vascularized and edematous. Mitotic activity gradually ceases. Earliest sign of secretory function

is the displacement of the glandular nuclei toward the lumen side of the cell, leaving a clear space at the basal portion. Globules of glycogen now appear within the cells.

In the *late secretory phase* (Fig. 180), the mucosa reaches a thickness of about 5 mm. The functionalis is now clearly demarcated from the *basalis*. Histologically, three strata are distinguishable. An innermost zone, the *basalis*, which makes up only one fifth of the endometrium, is composed of a dense cellular stroma containing the narrow basal ends of the

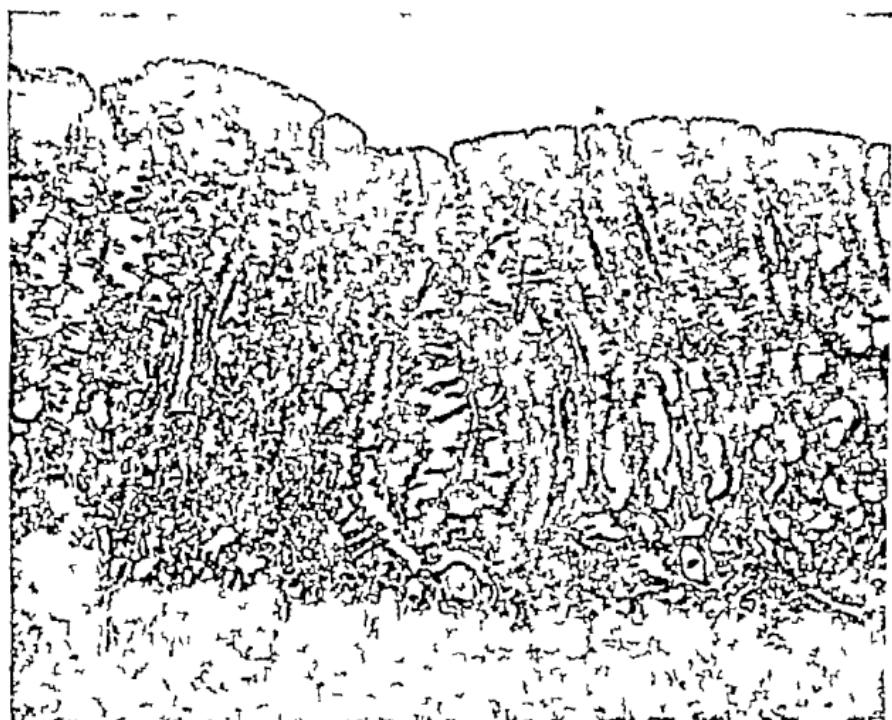


Fig. 180.—Pregravid endometrium. Microphotograph of tissue obtained twenty-seven days postmenstruum (Hoffman: Female Endocrinology).

glands; a middle zone or spongiosa contains the most dilated portions of the glands and comparatively little stroma; an outer zone or compacta, about half as thick as the spongiosa, lies immediately beneath the surface epithelium and is composed largely of edematous stroma harboring the relatively narrow terminal parts of the glands. It is during this phase that striking morphologic and functional changes become apparent in glands, stroma and blood vessels.

The glands, particularly those portions in the spongy layer, become sacculated and assume corkscrew or serrate formations. The columnar

cells lining them take on more glycogen and become distended with protoplasm. The nuclei are oval, stain palely and are more basally situated. As the secretions pour into the lumen, the free surface of the protoplasmic zone becomes increasingly irregular and eventually assumes a wavy, frayed, tuftlike appearance. The lumina of the glands become distended with fresh protoplasm containing glycogen. Their terminal parts, situated in the compact layer, are now more tortuous and actively secreting.

The stroma, especially that of the compacta, becomes progressively looser in texture. The cells take on much plasma, swell and become polygonal. Their nuclei are rounder and stain poorly. Towards the end of this phase, the stroma becomes markedly edematous and its cells often resemble decidual cells. The stroma of the spongy layer shows only a mild degree of edema which is most pronounced about the blood vessels.

The spiral arteries grow for a longer time than the other constituents of the mucosa, becoming increasingly tortuous throughout their length. They approach the surface rapidly, being found just under the surface epithelium at the height of this phase. Their walls, which are thin and contain very few nuclei during the proliferative phase, now widen, show an increased number of nuclei, stain less deeply and have a swollen appearance²⁷ (Fig. 181). That part of the arteries which traverses the spongiosa is of a larger caliber, more winding and has thicker walls, than in the compacta is less serpentine and more of a capillary nature. The capillaries in the compact layer are dilated and the capillary meshes spindle-shaped. In the spongy layer, they appear irregular due to the irregular form of the glands. The venous plexus in the functionalis shows an increased blood content. Venous lakes, larger and more numerous than during the proliferative phase, appear throughout the functionalis, being especially prominent in the border zone between the compacta and spongiosa. The basal veins share in the congestion.

THE CATABOLIC PHASE—Information regarding the sequence of events during the catabolic phase (Fig. 182) was, until recently, derived exclusively from studies of extirpated uteri and uterine curettings. Observers were aware of the essential changes which characterize the menstrual process but they could only surmise their exact sequence from the material at hand. Direct visual evidence was first obtained in the macaque by Markee,²⁵ who observed through a microscope the minute by minute and day by day behavior of intraocular endometrial transplants.

Briefly, Markee's observations were as follows. Growth of the endometrium slows down or ceases about five days before the onset of bleeding. Growth of the spiral arteries continues longer than that of the surrounding tissue, but always ceases at least thirty-six hours before hem-

orrhage begins. There is evidence of a reduced blood flow, soon followed by regression which begins from two to six days before bleeding and involves an appreciable reduction in the size of the transplant. The extent

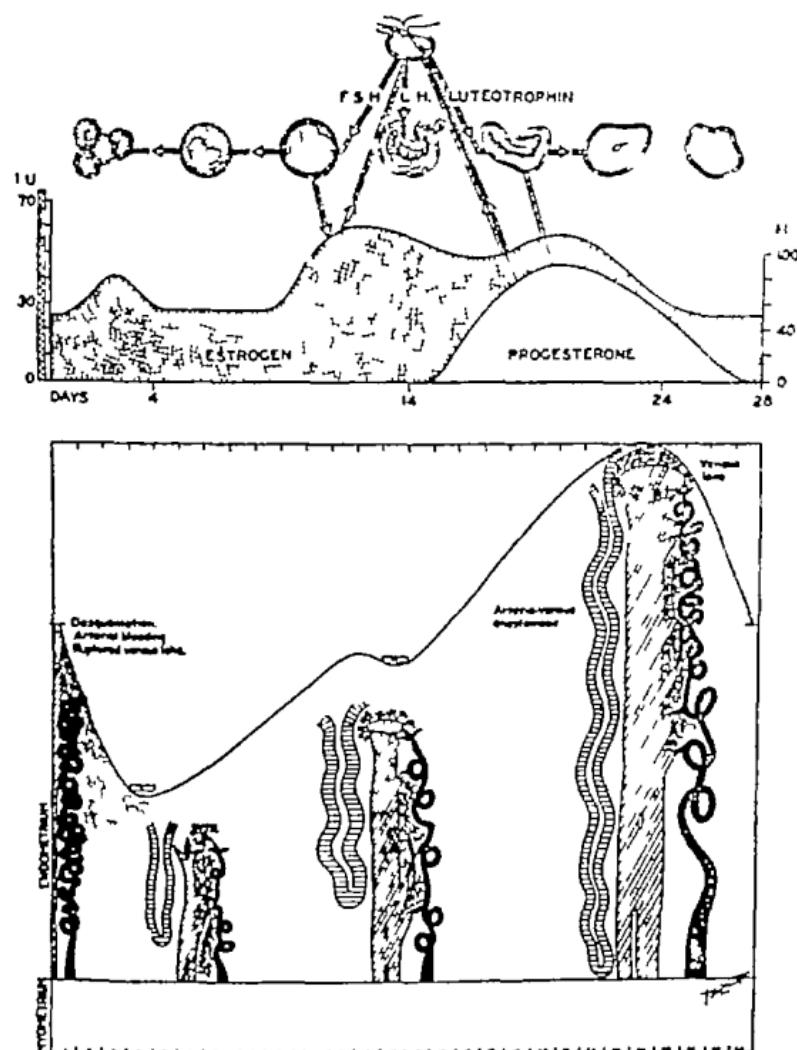


Fig. 181.—Schematic representation of the relation of cyclic vascular changes in the uterus to the chief hormonal factors with which these are associated (Reynolds in J.A.M.A. Vol 185)

of the reduction, achieved by the time hemorrhage begins, varies from 25 to 75 per cent and is apparently due to resorption of fluid. The resulting disproportion between the thickness of the mucosa and the length of the coiled arteries, which decrease little if at all, causes increased coiling

and shortens the distance between the surface epithelium and distal ends of the arteries

From one to five days before bleeding, at a time when the area of the transplant has been reduced 20 to 80 per cent, there is evidence of *stasis*. This varies in intensity according to the degree of coiling. Where the

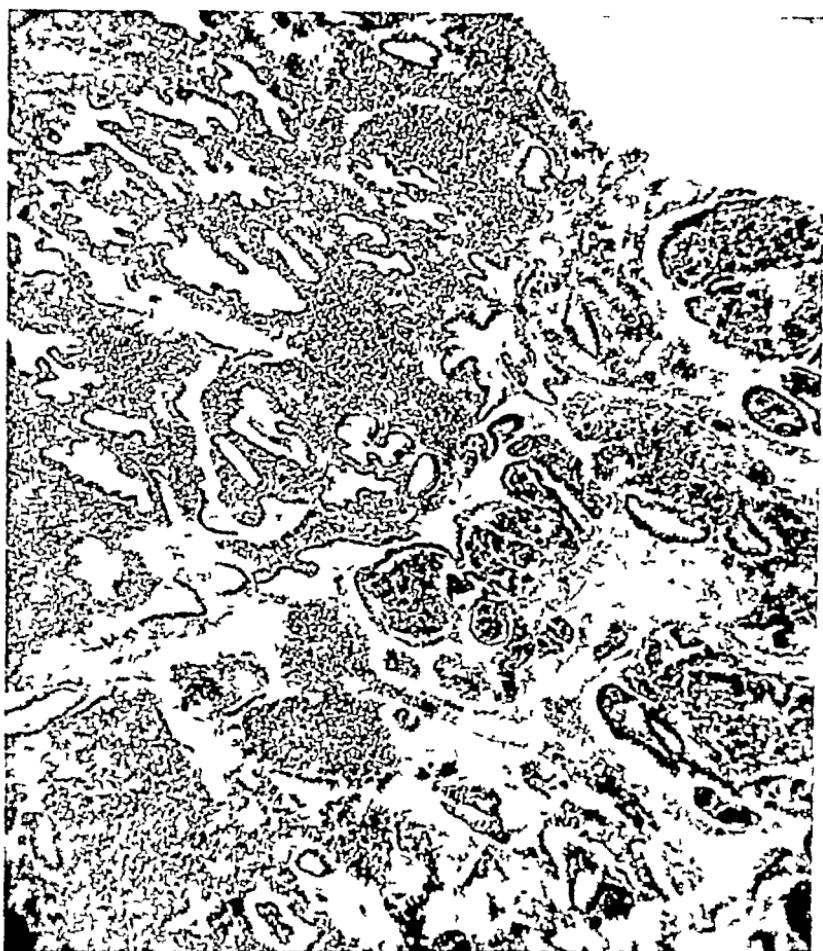


Fig 182.—Menstruating endometrium. Microphotograph of tissue obtained on first day of flow (Hoffman, Female Endocrinology.)

increase in the number of coils is sufficiently marked, stasis is associated with *vasodilatation*, but never with extravasation. During the period of stasis, certain areas become edematous due to the escape of plasma through the capillary walls. Leukocytic infiltration is a frequent but not a constant precursor of bleeding. When it appears, it precedes the bleeding by four days or less. The number of leukocytes escaping into the

stroma and glands is roughly proportional to the intensity of the vaso-dilatation and the completeness of the stasis. During this period there is evidence of degeneration of the stroma as well as the walls of the spiral arteries and their branches.

From four to twenty-four hours before bleeding the coiled arteries become *constricted*, one by one, the process occupying one to five hours in a given transplant. Obliteration of the lumen occurs in the deepest part of the basal zone. As a result the superficial half to two thirds of the endometrium, which is fed solely by these vessels receives an inadequate blood supply and appears anemic. A normal circulation persists in the basalis, whose arteries remain unchanged, and is partially maintained in the middle third of the endometrium, which is fed to a limited extent by the basal arteries.³

Hemorrhage begins when a constricted spiral artery relaxes and blood passes to its branches, escaping through a break in the wall of its arterioles or capillaries, or making its exit by diapedesis through the permeable capillaries. After reaching the stroma it may pass immediately out of the transplant or, in the absence of an easy exit, remains to form a hematoma which eventually ruptures. This type of bleeding usually occurs only once in a given area, being checked by contraction of the basal end of the artery. Soon after the flow of blood through the artery has stopped, its exposed end becomes necrotic. As relaxation and bleeding from individual arteries is repeated in different vascular areas of the transplant, the tissue becomes infiltrated with blood. This phase is usually not associated with loss of tissue.

Markee describes this type of hemorrhage as 'primary' to distinguish it from secondary hemorrhage which may follow fright or physical exertion. The latter follows the primary type and occurs through the branches of arteries which have achieved only partial or somewhat less than complete contraction. Complete contraction, as indicated by complete obliteration of the lumen in the basal portion of the artery, requires from one to twenty-four hours.

Hemorrhage from the arterioles and capillaries, by rhexis or diapedesis, accounts for about half the entire blood loss. Another fourth is lost through *venous hemorrhage* which begins later than the arterial bleeding. Two types are distinguishable. 'Direct' venous hemorrhage occurs when blood passes from a relaxed artery through an intact arteriole and capillary, and escapes through an opening at the superficial end of a vein. In the more common 'reflux' venous hemorrhage, the blood enters the deeper portion of the vein from the straight arteries in the basalis and flows in a reverse direction, escaping through an open superficial end. Venous hemorrhage occurs only where the vein has been opened by loss

or shedding of its superficial end and the tissue overlying it Venous bleeding is more prolonged than that through the arteries but, since it is much slower, only half as much blood is lost thereby

Near the end of the first day of bleeding in a transplant, *crumbling* of tissue begins An irregular fissure is seen extending inward from the surface Other fissures appear and separation is complete when they have completely encircled and undermined the fragment Crumbling is rarely seen during bleeding, occurring usually in regions where bleeding from a number of arterioles or capillaries has ceased Localized at first, it eventually becomes generalized Usually only one layer of larger fragments is shed Desquamation accounts for one-fourth or less of the decrease in the size of the transplant, from 75 to 95 per cent is due to resorption of fluid or involution of tissue The amount of tissue lost seems to be roughly proportional to the degree of coiling

Regeneration of the vascular system and of the epithelium over the denuded surface begins before bleeding from the transplant as a whole has ceased An artery, which has achieved complete contraction following the primary hemorrhage from one of its branches, shows evidence of necrosis in its exposed end within three to ten hours after contraction is complete Soon after its necrotic tip is plugged, its basal portion relaxes very gradually As blood enters this portion slowly, capillaries grow out from a point just under the necrotic end, which is shed shortly after this The new capillaries join the deeper portion of veins, whose superficial ends have collapsed and become obliterated

Arrest of bleeding from the transplant as a whole occurs only after a small amount of blood begins to circulate through the regenerated vascular bed in what remains of the functionalis

The "Bleeding Factor"—From the foregoing description of the catabolic phase, it would appear that regression is the first step in the chain of events culminating in bleeding That this process is initiated by hormone withdrawal is now generally conceded The identity of the factors which control the endometrial changes observed after this point, and the extent to which each of these alterations contributes to the production of hemorrhage, are still a matter of speculation

A view now gaining ground holds that, once regression has set in, the menstrual process is controlled within the endometrium It has been suggested that the stasis and vasodilatation, seen shortly after regression begins, is caused by the increased coiling of the spiral arterioles, which offer increased resistance to the flow of blood This finds support in Markee's observation²⁵ that the intensity of the stasis and length of the period of vasodilatation is roughly proportional to the increase in the number of coils On the other hand, Keiffer²⁸ ascribes the dominant role

in producing the characteristic vascular changes incident to menstruation to "venous hearts," valvular and contractile modifications of the venous walls, which show rhythmic dilatation and contraction related to the contractions of the uterus as a whole. The importance of myometrial activity is stressed by Westman,²⁹ who believes that contraction of the uterine muscle, following withdrawal of luteal influence, causes hyperemia and stasis, while Marlow³⁰ suggests that in the premenstrual phase, while the high pressure arterial system distributes blood to the endometrium, the low pressure valveless venous outflow system becomes more and more embarrassed because of myometrial grasp." Bartelmez³¹ has also conceded the possibility that venous drainage may depend on rhythmic contractions of the uterus which, if retarded or inhibited before menstruation, may conceivably cause venous congestion. Though the variations in myometrial activity which occur in the uterus *in situ* shortly before and during menstruation undoubtedly exert some effect, it can hardly be considered crucial in view of the fact that the changes described by Markee³² occurred in intraocular transplants, where myometrial activity is minimized, if not completely excluded.

To account for the superficial ischemia which is a constant and immediate precursor of hemorrhage, several possibilities have been considered. Daron³³ found cone shaped constrictions of the spiral arteries in the inner fourth of the myometrium, which he attributed to active contraction. He suggests that they may be homologous to the endothelial cushions or "polsters" observed in the uterine arteries in man and found to be abundant in the inner zone of the myometrium next to the endometrium.³⁴ Markee³⁵ found that constriction occurred in the deepest portion of the basal zone. He argues that this is due, not to passive compression but to active contraction, as borne out by the fact that contraction is followed by relaxation and again by contraction in individual arteries.

The possibility that the cause of this constriction is pituitrin, product of the posterior hypophysis, has been eliminated by the observation that menstrual bleeding is not prevented by hypophysectomy³⁶ and cannot be brought on prematurely by pituitrin injections.³⁷ That the vasoconstrictor may be of endometrial origin was first suggested by Markee.³⁸ He proposed that degeneration of the mucosal tissue, which is seen to precede vasoconstriction, gives rise to a toxin, to which the spiral arteries react with constriction. His suggestion that some of this toxin is absorbed and enters the general circulation would account for the observation³⁹ that spasm of the skin capillaries occurs premenstrually at approximately the same time that vasoconstriction takes place in the endometrium. Support for his theory has recently been provided by Smith and Smith⁴⁰ who extracted from the catamenial discharge a toxic protein which is most

concentrated in the endometrial debris and is demonstrable in the circulating blood during but not between the flows. It is lethal to rats and rabbits and causes local and systemic reactions characterized by edema, hemorrhage and necrosis like that in the menstruating endometrium. They interpret it as a component of the endometrial cells split off during their catabolism resulting from hormone deprivation. Finding it identical with "necrosin," a substance extracted from the pleural exudate of dogs injected with turpentine,³⁶ they conclude that its formation follows tissue injury, whether in the endometrium or elsewhere. Whether this or an associated by-product of endometrial disintegration is responsible for vasoconstriction is a question which must await experimental demonstration of this effect in intraocular transplants.

The importance of arteriovenous anastomoses as a cause of the superficial ischemia and consequent necrosis which precedes menstrual bleeding has recently been stressed by Schlegel²¹ and Dalgaard.²² The former suggests that the explanation of menstruation may be found in these anastomoses, vasoconstriction being a secondary phenomenon brought about by necrobiosis. He theorizes as follows. Under the influence of the ovarian hormones, the number of arteriovenous anastomoses increases with the general vascular development, increasing the number of short circuits between the arterial and venous systems. This in turn means that the irrigation coefficient must rise, since otherwise the superficial capillary supply will be compromised. At a given point, a disproportion arises because the ovarian hormones are unable to further raise this coefficient. The result is shunting of the blood away from the peripheral capillary bed, with consequent necrosis of the superficial layer and hemorrhage. Congestion of the extensive venous lakes in the subepithelial levels of the mucosa also contributes to this result.

Dalgaard offers a somewhat different explanation. He proposes that the arteriovenous anastomoses be regarded as the regulator of changes in the blood content of the arterioles and venous lakes which they serve to join. Since they occur just under the superficial zone, their activity would limit blanching of the endometrium to its superficial layer. Such blanching occurs when closure of the anastomoses results in involution of the subepithelial venous lakes. His theory would imply that the arteriovenous anastomoses are supplied with a form of constrictor apparatus. He fails, however, to demonstrate such an apparatus or to identify the stimulus responsible for its closure premenstrually. According to Schlegel, the arteriovenous anastomoses show no particular closing mechanism.

To what extent each of the vascular changes, observed premenstrually, contributes to the causation of bleeding is still unsettled. Since non-menstruating species fail to show the coiling of the arteries, stasis and

vasoconstriction observed in primates, it is natural to seek in these phenomena the answer to why only primates bleed. The importance of coiling seems questionable in view of the fact that hemorrhage occurs in the anovulatory cycle, where growth of the spiral arteries and the degree of coiling during regression is comparatively limited and in New World monkeys which lack spiral arterioles. The role of the arteriovenous anastomoses has been questioned on the same ground.²⁷ That vasoconstriction per se is not the cause of hemorrhage is indicated by the failure of attempts to induce menstruation prematurely with vasoconstrictor substances.^{27, 28} Nor can ischemia alone account for menstrual bleeding, in view of the observation that castrate monkeys, receiving a constant supply of estrogen, fail to bleed despite ischemia of the entire uterus produced by ligating both ligaments.²⁷ At best, therefore, these phenomena may be said to play only an accessory role, along with other more fundamental alterations. Increased coiling undoubtedly helps promote disintegration and at the same time to prevent excessive blood loss. Vasoconstriction, as pointed out by Markee,²⁶ is to be interpreted not as the cause of menstruation but rather as a defensive mechanism against excessive blood loss from injured vessels. The work of Smith and Smith²⁹ identifying their menstrual toxin with "necrosin" suggests that this substance may not be considered a specific menstrual bleeding factor. In this connection, Meyer³⁰ has pointed out that the appearance of ischemia is a preliminary disturbance in almost all forms of necrosis, pathologic and experimental. Reynolds³¹ has recently suggested that the answer may lie in the absence of lymphatic capillaries in the superficial fourth of the endometrium. The subepithelial edema with attendant necrosis and desquamation may be associated with a deficient mechanism for the removal of plasma proteins from interstitial spaces. Experimental support for this is still lacking.

Though the available evidence does not justify any final conclusions, it seems likely, in view of the negative effects of experimentally induced vasoconstriction and ischemia, that the fundamental change indispensable to the occurrence of bleeding and desquamation is loss of appropriate hormonal support. The endometrial structures built up by the ovarian hormones are apparently dependent on these hormones as much for maintenance as for their original growth. Their continued integrity requires, in addition to the usual nutrient supplied by an adequate circulation, the support of these hormones, which may conceivably be needed to enable the newly constructed tissue to utilize that nourishment. If the primary role in the maintenance of mucosal integrity is allotted to the ovarian hormones, then degeneration of the endometrial tissue must be considered crucial in the causation of menstruation, other

changes noted being secondary. That such degeneration should culminate in a hemorrhagic type of desquamation only in the primate may be due to the peculiar vasculature of the primate uterus and its peculiar response to the need for a nidatory bed. To quote Meyer²⁹ "The endometrium, in preparing for pregnancy, must progress to a stage adequate for the varying degrees of aggressiveness of the chorion specific to every species. In the primate, the decidua and its vessels are developed to a remarkable degree in order to satisfy the angiotactic demands of the fetal chorion." It is significant that the baboon, in which arterial development is less extensive than in the macaque, bleeds less, while the New World monkey, which lacks spiral arterioles, shows only microscopic bleeding. Recalling that in some cycles in the macaque, as much as 95 per cent of the reduction of the mucosa is accomplished by resorption of fluid and tissue involution, and in view of evidence that gradual hormone withdrawal may cause regression without bleeding, it is not difficult to imagine a transition to a condition where a less extensive vascular tree and a more gradual withdrawal of hormonal support would result in a nonhemorrhagic type of endometrial involution. A final answer awaits further investigation.

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THE PROPER MANAGEMENT OF FUNCTIONAL MENSTRUAL DISORDERS

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THE PURPOSES OF TREATMENT

In attempting to select the proper approach in the treatment of patients with functional disturbances of menstruation a broad viewpoint is desirable. It is constantly necessary for the physician to be cognizant of the fact that such disturbances represent only a symptom of some underlying condition. It is true that in some instances, particularly those associated with excessive bleeding, symptomatic therapy may be urgent, but failure to pursue the matter further may prove to be a serious or embarrassing oversight. In other cases, as in some women with amenorrhea, the question as to whether any therapy at all is indicated requires careful consideration.

Indeed, the kind of treatment which the physician chooses is influenced by many factors, not the least important of which are those of maintaining normal fertility and normal endocrine function of the ovaries. The evaluation of these factors entails, first of all, a sufficiently thorough study of the patient to indicate the basic etiology of the menstrual disorder. If this proves to be a symptom of a systemic disease it is, of course, the latter to which therapy should be directed, and the cure of the symptom will follow. On the other hand, if the menstrual symptom is an expression of a primary ovarian deficiency not related to any other demonstrable cause the decision to treat is dependent upon the age of the patient, her desire for future pregnancies and also the associated symptoms of her condition. If the woman has had her family, or is not desirous of pregnancy, and if in addition she feels well in every respect, is the effort to induce cyclic bleeding of any value, except perhaps for its psychologic effect, and may it not be better to help such a patient reach a state of good adjustment without therapy for the amenorrhea? In contradistinction is the younger woman who has developed a secondary amenorrhea of similar origin but whose great hope is to have children, here the treatment of amenorrhea is part and parcel of the infertility problem and of course justifies the use of every reasonable therapeutic effort. A more

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difficult decision to make arises in the patient in whom fertility is not a factor but who is certain that she "feels better" when she has a menstrual period.

In patients with bleeding excessive in amount, duration or frequency, symptomatic therapy is often essential because of the effects of blood loss. After the immediate bleeding problem has been controlled, thorough evaluation of the etiologic factors must be pursued and more rational therapy instituted in order to prevent recurrence. Although the control of excessive bleeding generally is the prime immediate purpose of treatment in such patients, the fertility problem again plays an important place in determining the type of treatment. In the postpubertal girl with recurrent uterine hemorrhage of dysfunctional origin, both the patient and the physician are willing to go to all reasonable lengths to prevent hysterectomy or even irradiation therapy, whereas in the woman with functional bleeding at the menopause, either of the latter methods of therapy is frequently acceptable and offer the most satisfactory solution to the problem.

In addition to the control of excessive bleeding and the cure of infertility as manifestations of menstrual disorders, the physician frequently finds it necessary to deal with the relief of associated pain. There are few problems which are more vexing than the management of severe dysmenorrhea when it is not associated with demonstrable local disease, since in the light of our present knowledge "primary" or "essential" dysmenorrhea must be regarded as a symptom-complex occurring in an otherwise normal cycle. Indeed, many gynecologists regard dysmenorrhea of this type as good evidence that ovulation has occurred in that particular cycle. For this reason the most commonly accepted forms of therapy are those which are symptomatic, making use of analgesics, sedatives and antispasmodics. The most effective methods to prevent the dysmenorrhea usually depend upon producing an abnormal cycle, such as the inhibition of ovulation with high dosage estrogens or androgens, their use therefore requires careful consideration as do certain recommended surgical procedures such as presacral neurectomy.

There are, in addition, patients with various menstrual molimina some of which are quite common such as "premenstrual tension," migraine and mastalgia, others of which are quite unusual such as premenstrual ulcerations of mucous membranes, "allergic" phenomena, fever, extreme edema and the like. Careful evaluation of the severity of the symptoms, the underlying etiologic factors, as well as the undesirable effects of any contemplated plan of therapy must guide the physician in determining the best method of approach.

EVALUATION OF ETIOLOGIC FACTORS

A proper evaluation of the factors which influence menstrual function depends upon an appreciation of the basic physiology of the normal menstrual cycle, this subject has been reviewed in a separate clinic of the present volume (page 1485). It is apparent from the nature of the underlying mechanism that functional disturbances culminating in abnormalities of menstruation may arise in many spheres including those primarily in the uterus itself, those directly involving the function of the pituitary and the ovaries, as well as numerous disorders which may disturb normal pituitary, ovarian or uterine physiology, such as systemic diseases, metabolic disorders, various endocrine dysfunctions both gonadal and extragonadal, hematologic disorders, psychogenic upsets and even environmental changes.

The character which the menstrual dysfunction will assume depends upon many factors. In the earliest stages of a general disturbance influencing the pituitary-ovarian cycle it may be postulated that failure of ovulation occurs first, since the maturation of a follicle and the release of a fertilizable ovum represent the acme of perfection in pituitary-ovarian function. *Anovulatory sterility*, therefore, may be considered as a type of menstrual dysfunction despite the fact that for some time the flow itself may be normal in periodicity, duration and character, although not infrequently minor changes are noted by the patient from the very beginning. As ovarian function further diminishes, either as the result of inadequate gonadotrophic stimulation or inability of the ovary to respond to even excessive gonadotrophin production, *hypomenorrhea* and *oligo-menorrhea* may result and, finally, as ovarian function further declines, amenorrhea results. If estrogens are produced in irregular spurts with sharp but unsustained rises, *irregular bleeding* results. It is probable that the character and severity of the bleeding in the latter condition is dependent not only upon ovarian function but also the 'responsiveness' of the endometrium and, particularly, the spiral arterioles of the endometrium.

Local Organic Factors.—The diagnosis of functional uterine bleeding is one which must be made by exclusion if malignancies and other serious lesions are not to be overlooked. In every instance, therefore, it is necessary to prove by appropriate diagnostic procedures, including when necessary diagnostic curettage, biopsy or even laparotomy, that an organic lesion is not the primary source of the disturbance. Not infrequently repeated careful pelvic examinations will eventually disclose findings indicative of an organic lesion which could not be determined on the initial examination. Moreover, it is not at all rare to find such lesions

at laparotomy, which were not suspected on examination, in patients who have been treated for a long period on a functional basis but who failed to make an adequate response. It must be borne in mind that what seem to be relatively minor local pelvic factors may, in some instances, give rise to persistent menstrual dysfunctions, so that every effort should be made to correct such disturbances, among these may be included inflammatory lesions of the cervix, some instances of marked retroversion of the uterus in parous women, low grade pelvic inflammatory disease and the like. Not infrequently the correction of minor abnormalities which appeared to be of little moment may yield very gratifying results in the correction of "functional" menstrual disorders.

Constitutional and Systemic Factors — In most women the sex-endocrine cycle is very labile and is one of the physiologic functions earliest to react to unfavorable factors in either the soma or the psyche. In some instances the disorder may be transient and of little practical consequence, such as those minor menstrual disorders which may in some women accompany acute infections, increasing obesity, too rapid loss of weight by dieting or a change in climate or surroundings. When the underlying disease is more serious or prolonged or the psychogenic trauma more deep-seated, the effect on the sex-endocrine cycle is likewise more profound. Thus a menstrual disorder may occur as one of the earliest manifestations of such diverse conditions as tuberculosis, leukemia or anorexia nervosa.

Menstrual disorders which result from general or systemic factors operating through the pituitary-ovarian mechanism may manifest themselves in a diversity of forms such as *amenorrhea* or *hypermenorrhea*, *oligomenorrhea* or *polymenorrhea*, *irregular bleeding* or even as regular but *anovulatory bleeding* with associated *infertility*. In some instances the menstrual cycle may be affected through the pituitary while in other cases it may be the ovary which is primarily disturbed. So far as the menstrual manifestations are concerned these may be the same in either case, although some of the associated symptoms may be different. In primary ovarian deficiencies, for instance, hot flashes are a frequent accompaniment. In many instances, however, it is not possible to tell by which mechanism ovarian dysfunction is being suppressed *except by gonadotrophin assays*, the urinary excretion is absent in the "pituitary" cases and excessive in the primary ovarian deficiencies. Odd, as it may seem, is the fact that the same disease or disorder in some women may cause inhibition of the ovaries while in others it may suppress the gonadotrophic function of the pituitary. Little is known concerning the mechanism by which either of these is accomplished. It is postulated that pituitary inhibition is accomplished over pathways from the cerebral cortex and spinal centers to the hypothalamus and the pituitary, while suppression

of the ovary results from stimuli coming over sympathetic nerve fibers to the ovary. Much remains to be learned concerning these important neuro-endocrine relationships.

Endocrine Dysfunctions of the Pituitary and the Ovary—True endocrine diseases of the pituitary and ovary are relatively rare as causes of menstrual dysfunction in comparison to the common pituitary-ovarian dysfunctions which occur as secondary manifestations of general disturbances.

In pituitary tumors of all types including basophilic tumors (Cushing's syndrome), eosinophilic tumors (giantism and acromegaly) and chromophobe tumors, amenorrhea sooner or later results although it may be preceded by a period of hypermenorrhea, polymenorrhea or menstrual irregularity. Similar menstrual dysfunctions also occur with other destructive lesions of the pituitary (Simmonds disease), or may follow interference of pituitary function by other intracranial lesions or hypothalamic diseases.

Endocrine or functioning tumors of the ovary, whether of the feminizing or masculinizing type, sooner or later generally result in amenorrhea, but also may be preceded by a period of menstrual irregularity or episodes of profuse bleeding. In the feminizing tumors, such as the granulosa cell and the theca cell tumors, the menstrual disturbance is associated with various manifestations of hyperestrogenism, while in the masculinizing tumors atrophic changes in the genital organs and masculinizing effects are present. Whether the common non neoplastic cystic diseases of the ovary should be classified as an endocrine dysfunction is a mooted problem. Small cyst degenerations of various kinds, and even the larger functioning or physiologic cysts of the ovaries, are commonly associated with menstrual irregularity and so-called 'functional' uterine bleeding. From an endocrine standpoint they are generally associated with irregular pituitary gonadotrophin excretion, high estrogen production and often diminished or absent progesterone production. It is the opinion of some authorities that these lesions are secondary to other causes which have produced repeated insults to the ovary, while others believe that they represent a primary endocrine defect.

Extragonadal Endocrine Dysfunctions.—Marked disturbances of thyroid dysfunction are well known to influence the menstrual cycle. It is postulated that the thyroid may influence pituitary ovarian function primarily by its effect on pituitary. In hypothyroidism there is generally an excessive outpouring of pituitary thyrotrophic hormone which may perhaps drag with it the pituitary gonadotrophins. On the other hand, in hyperthyroidism the excessive amount of thyroid hormone may act as a depressant to pituitary function.

In cretins pubescence is delayed and amenorrhea is quite common. Menorrhagia frequently occurs in women who develop myxedema, though other types of menstrual dysfunctions are also found, including amenorrhea or irregular bleeding. Patients with hypothyroidism tend to be less fertile and when they do become pregnant the incidence of abortion appears to be increased. In women with hyperthyroidism episodes of amenorrhea and oligomenorrhea are more common, although again irregular or profuse bleeding may also be noted. If the hyperthyroidism is not severe, normal menstrual function may persist and fertility may also be normal, as a rule, such hyperthyroid patients do fairly well during pregnancy.

In adrenal cortical dysfunctions the effect on menstrual cycle results chiefly from the disturbance of the estrogen-androgen balance. In most female patients with adrenal cortical hyperfunction the adrenal produces excessive androgens, thus resulting in masculinization and, because of the depressing effect upon the pituitary, amenorrhea also generally follows. In hypofunction of the adrenal cortex, such as in Addison's disease, oligomenorrhea and amenorrhea are frequent, probably resulting from diminished pituitary-ovarian function consequent to debility.

The disturbance in sex endocrine function which occurs in severe diabetes is well known but not well understood. In those young diabetic patients with sexual infantilism and amenorrhea whom we have had an opportunity to study, we have found diminished pituitary gonadotrophin and, in some instances, have been able to establish cycling by administering gonadotrophic hormones.

Metabolic Factors—The importance of nutritional and metabolic disturbances in menstrual abnormalities has been recognized for many years, although we are now gaining better insight into the specific factors which are essential, comparatively little is known of the *modus operandi*. Apparently the absence of certain essential foodstuffs can influence pituitary-ovarian function as indicated by the amenorrhea which has been noted in malnourished groups, especially during war periods. Also attention has been focused by some workers on certain members of the vitamin B-complex, particularly thiamine and riboflavin, as necessary for "inactivation" of the estrogens. Normal function of the liver appears to play an important role in the intermediary metabolism of the ovarian hormones, in cirrhosis of the liver particularly, menorrhagia, dysfunctional uterine bleeding, endometrial hyperplasia and premenstrual tension occur quite commonly. Only a beginning has been made in understanding the enzyme systems involved in the metabolism and inactivation of the ovarian hormones.

METHODS OF THERAPY THEIR VALUE AND THEIR LIMITATIONS

General 'Hygienic' Measures—It is customary to begin the discussion on the therapeutic approach to most diseases by pointing out the value of such measures to improve the general state of health of the patient as physical rest, mental relaxation, improved nutrition, supplementary vitamins and various tonics. These have in the past been the mainstay in the treatment of functional menstrual disorders, particularly in the years before more exact methods for study were available and the present hormonal medications were introduced. There can be no question of the usefulness of these methods of approach, then or today, since in so many women disturbances of the pituitary-ovarian uterine mechanism may be markedly affected by anxiety or fatigue. Moreover, disturbances of menstruation not infrequently are early manifestations of other minor illnesses which may be cured by rest alone. On the other hand, it is self-evident that in a goodly proportion of cases these measures alone, even under the best of circumstances, will fail to effect a cure. A good evaluation of the underlying etiologic factors will do much to enable the physician to pass judgement as to which patients will require more specific treatment. Other factors which also influence this decision are the urgency of the symptoms, as well as matters of economy and time.

Endometrial Curettage.—Curettage of the uterus is a doubly useful weapon in the management of uterine bleeding in that this procedure, which is so often necessary for diagnostic aid, not infrequently proves to be of therapeutic value in addition. As a diagnostic technic it is often essential in order to differentiate organic lesions from functional causes, and even in the event of the latter it frequently furnishes significant information helpful in establishing a more accurate diagnosis. As a therapeutic aid it is of especial help in terminating episodes of excessive bleeding, in cases of irregular bleeding it is on occasion gratifying to find that normal menstrual rhythm may be established after curettage. The mechanism by which this occurs is not known but may be attributed to the stimulation of a neuro-endocrine mechanism from the uterus to the pituitary, there is evidence of such pathways in some animal species, particularly the rabbit. In dysmenorrhea, dilatation of the cervix followed by curettage also occasionally furnishes relief, although generally of rather limited duration.

Psychotherapy—This approach to treatment is mentioned at this point because it is increasingly apparent that a large proportion of menstrual dysfunctions can be attributed to emotional disturbances. Women who menstruate regularly but fail to become pregnant until a problem at home has been settled or a baby has been adopted are common examples.

of a type often amenable to reassurance and simple psychotherapeutic measures given by the family physician. When the problem has become so deep-seated as to produce amenorrhea or dysfunctional bleeding, more intensive psychotherapy is necessary. In some instances the results are brilliant, although the percentage of success is not so great as might be desired, perhaps because sufficiently intensive treatment is often not possible because of factors of time and money. It might be added, however, that the patients most resistant to psychotherapy are also often the most resistant to hormonal and other methods of treatment.

Thyroid Therapy—Thyroid extract has for many years been the most widely used endocrine preparation for the treatment of functional menstrual disorders and infertility and, indeed, has been referred to as the "sheet-anchor" in the management of such conditions. It attained its popularity partially owing to the fact that for many years no other hormonal preparations were available and thyroid as a consequence was given a "trial." Frequently it is used empirically in patients in whom there are no clinical manifestations of hyperthyroidism and in whom the basal metabolic rate is not significantly diminished. In some instances good results have been noted despite the fact that no real rationale for its use in such cases is known.

It may well be conjectured that thyroid extract exerts some beneficial effects even in the absence of hypothyroidism, the nature of which are not at present known. On the other hand, it is also true that the indiscriminate use of thyroid may lead to harmful results. Moreover, the practice of giving thyroid routinely, as a therapeutic trial, without making further investigations to determine the true nature of the dysfunction is to be discouraged. In our opinion the regular use of thyroid extract should be limited to those instances in which there are clinical and laboratory evidences to indicate thyroid deficiencies. There can be no question that in such cases results with thyroid are indeed excellent, whereas the result in euthyroid individuals is, in our experience, not generally beneficial.

Vitamin Therapy—Various members of the B-complex, particularly thiamine and riboflavin, have been rather extensively administered especially on the basis of the claim of the Biskinds and their co-workers² that these factors are essential for the proper inactivation of the estrogens by the liver and that their deficiency may cause such manifestations of hyperestrogenism as menorrhagia, hyperhormonal amenorrhea, premenstrual tension, cystic mastitis and the like. In these conditions the oral administration of thiamine and riboflavin in the magnitude of 50 mg of each daily is recommended. The present author must confess that his results with this type of therapy have been disappointing.

Vitamin E has long been suspected of serving an important function in human gonadal physiology, particularly because it seems to be essential for normal fertility in the rat. Its extensive use during the past decade in human male and female infertility has not shown it to be efficacious in the hands of most workers, but claims of benefit by some workers still appear. Recently the use of the natural tocopherols in high dosage, such as 100 to 150 mg daily, has been suggested in the treatment of the menopausal syndrome, particularly where estrogens are contraindicated. In this condition it appears to be of limited usefulness in the control of very mild vasomotor symptoms, it does not appear to influence disturbances of menstrual flow.

Oxytocics.—Ergot and its derivatives, as well as pituitrin or its oxytocic fraction, pitocin, are much more frequently used in the treatment of functional uterine bleeding than critical analysis of their effectiveness justifies. These preparations, which act by contracting the uterine musculature, are of much help in excessive bleeding associated with postpartum subinvolution of the uterus. In other types of functional bleeding, where the source of bleeding is from the spiral arterioles with no associated disturbances in the myometrium or its blood vessels, it is questionable whether oxytocics serve any useful purpose. Indeed, in some instances these preparations are followed by crampy pains and a temporary increase in bleeding.

Hormonal Therapy—The gonadotropic and gonadal hormones are the most specific gynecologic medications at the physician's disposal for the treatment of many functional disorders. Critical judgement, however, is frequently necessary to determine whether their administration is the best approach in individual patients with menstrual disturbances. Their indiscriminate use for symptomatic therapy is to be discouraged, not only because it favors the temptation of "doing something" without making an adequate diagnosis but because, if used improperly, such preparations may further complicate the condition; they are potent medications and are capable of inducing untoward as well as helpful reactions. Even when diagnostic procedures have been carried out which would indicate the mechanism of the disturbed endocrine physiology, good judgement is required in determining whether the disturbance is a primary endocrine one or simply secondary to other factors to which therapy should be directed.

These precautions are emphasized not to minimize the importance of hormonal therapy but rather to prevent these useful medicaments from being discredited by their misuse. In this regard it would perhaps not be amiss to point out that hormonal therapy is used with most caution by those who have worked the most with these medicaments. However,

when properly used in the proper cases the results with hormonal therapy often afford the most satisfactory solution to the problem at hand

Space does not permit describing the details of rational hormonal therapy of menstrual disorders, indeed, the latter is the title for an earlier presentation by this author in these clinics¹ to which the reader is referred Our present purpose is to point out the broad general indications and contraindications for the various hormones used in the treatment of menstrual dysfunctions

GONADOTROPHIC HORMONES—*Follicle-stimulating gonadotrophic substances* (pituitary gonadotrophin, equine or pregnant mare serum gonadotrophins, "synergistic" gonadotrophin mixtures) are employed where there is a deficiency or irregular production of pituitary gonadotrophins causing amenorrhea, anovulatory sterility or dysfunctional uterine bleeding The best results are obtained in patients with excessive bleeding, the results are comparatively poor in the amenorrheic patients Some degree of success is obtained in anovulatory sterility with intensive therapy given during the follicular phase Gonadotrophic therapy should be avoided in women approaching or beyond the menopause and also in younger women with cystic disease of the ovaries or other ovarian enlargements It should be given in cyclic fashion during the first two or three weeks of the cycle, never continuously through the entire cycle

Chorionic gonadotrophin is rarely of help in these conditions Given in high dosage during the last half of the cycle it is sometimes of aid in menstrual dysfunctions attributable to poor or inadequate corpus luteum function

Prolactin has in recent years been regarded as a third gonadotrophic hormone (luteotrophin) Given in adequate dosage it is sometimes useful in controlling functional menorrhagia, especially when the latter is thought to be due to inadequate corpus luteum function It may be given alone or in conjunction with chorionic gonadotrophin

ESTROGENS—On a rational basis, estrogens are indicated in those patients who have a primary ovarian dysfunction In such instances the hormone is used to overcome the symptoms of the primary estrogen deficiency, to inhibit excessive pituitary function, to permit the ovary a period of physiologic rest, and to induce cyclic bleeding If the ovary has not been damaged by organic disease it is possible in some instances to restore normal ovarian function after some months of cyclic estrogen administration On the other hand, in some patients who appear to be free of any local or constitutional diseases, repeated and prolonged estrogen therapy is of no permanent avail, often such patients are found to have marked psychogenic disturbances as the basis for their trouble

It is our opinion that, as a rule, high dose estrogen therapy should not

be used as a routine procedure in the treatment of functional bleeding. The practice of administering huge dosages of estrogens by mouth or by intramuscular injection with the aim of producing sudden cessation of bleeding not infrequently gives rise to further bouts of hemorrhage even though a favorable initial response is sometimes obtained. When estrogens are employed we prefer generally to administer them in physiologic dosages, in cyclic fashion, and with added progesterone in the last half of the cycle.

In the treatment of the menopausal patient, estrogens are specifically indicated if the syndrome is sufficiently severe to cause distress, and if mild sedation and psychotherapy have failed to be of sufficient benefit. It is also a good rule that estrogens should never be administered without a previous careful pelvic examination and that they be withheld if the pelvic organs are not entirely normal. It is to be emphasized that small fibromyomas may grow during the course of estrogen therapy. It is also advisable that estrogens should be given only to those menopausal patients who have a clear-cut menstrual history of either amenorrhea or normal cycling, since irregular bleeding beginning during the course of estrogen therapy may mask malignancy if attributed to the medication alone.

Estrogens are of some value in the treatment of essential dysmenorrhea if given in sufficiently high dosage to inhibit ovulation. They should be used only for a period of two to three months for this purpose, being employed to give temporary relief of pain, as an aid in establishing the diagnosis of primary dysmenorrhea, and perhaps in causing some growth of the uterus. In most instances the dysmenorrhea returns after treatment is discontinued but some degree of lasting benefit is obtained in occasional cases.

Estrogens are of limited usefulness in the treatment of premenstrual tension, menstrual migraine and cystic mastitis. The effects are likely to be more helpful in patients approaching the menopausal years than in younger women with these complaints.

PROGESTERONE—Progesterone has become an increasingly valuable hormone in the treatment of functional disturbances of menstruation. In addition, its usefulness has been extended by the fact that it is less likely to cause untoward effects when given in adequate dosage than any other hormonal preparation. In the treatment of functional menstrual disorders progesterone has a potent 'regulating' effect on the pituitary ovarian cycle. The manner in which the latter is accompanied has not been fully worked out, however, there is some evidence to indicate that progesterone causes the formation of a substance in the endometrium, termed the menstrual toxin by the Smiths, which is thought to be

"stimulating" to the pituitary and thus favors better pituitary gonadotrophic function. There is also reason to suspect that it may have a favorable effect upon ovarian "responsiveness."

From a practical standpoint, progesterone given in high dosage finds its greatest usefulness in the treatment of amenorrhea of functional origin. It appears to work equally well in patients with primary ovarian defects or with primary pituitary deficiencies. If the amenorrhea is of relatively recent origin, progesterone given in a dosage of 20 mg by injection on three consecutive days will usually cause withdrawal bleeding four days after the last injection. This therapy can be continued through three consecutive cycles after which it may be withdrawn to determine whether spontaneous cycling will follow. If the patient has long-standing amenorrhea it is frequently necessary to prime with estrogen for several weeks before giving progesterone, or, as suggested by Zondek,⁴ estrogen and progesterone may be given together by injection in high dosage over a period of two to five successive days.

Progesterone is of comparatively little value in stopping an episode of functional bleeding, however, once the bleeding has been brought under control, progesterone given in moderate dosage by injection such as 5 mg twice weekly, or by mouth in the form of anhydrohydroxy progesterone, 10 mg daily, during the last ten days of the cycle, will frequently prevent a bout of menorrhagia in the succeeding cycle.

Progesterone is not often helpful in the treatment of dysmenorrhea, on occasion, brilliant results are obtained with 20 mg of anhydrohydroxy progesterone given daily for the ten days preceding menstruation. Usually progesterone should not be used in the treatment of premenstrual tension since ordinarily it may increase or exaggerate most of the premenstrual symptoms particularly bloatedness, nervousness and irritability.

TESTOSTERONE—Androgens have come to occupy a place of considerable importance in the treatment of menstrual dysfunctions. If it were not for the arrenomimetic effects of large dosage of androgens, or those which follow from the long-continued administration of smaller dosages, the androgens would have indeed a very wide field of approach in the management of excessive bleeding as well as for the relief of many menstrual molimina.

The androgens may be considered to be "anti-estrogenic" in view of the fact that they inhibit ovarian function. This inhibition probably is produced by the effect of testosterone on the pituitary but there are also some reasons to believe that testosterone may have some direct inhibiting effect upon the ovary as well, and furthermore, the androgens appear to have a direct atrophying effect upon the endometrium.

Testosterone finds its chief application in the control of excessive uterine bleeding of functional origin. For this purpose it may be given by

injection in the form of testosterone propionate or by mouth in the form of methyl testosterone. In some instances testosterone may also be used for further treatment in preventing recurrences of menorrhagia. For this purpose it is generally given for ten days or two weeks preceding the flow.

For the control of severe premenstrual tension, testosterone probably is the most useful of the hormonal preparations. For this purpose methyl testosterone may be given cyclically from the fourteenth to the twenty-fourth day of the cycle by mouth in a dosage of 5 to 10 mg daily. In cystic mastitis or premenstrual mastalgia testosterone may be used in similar fashion. It is also to be pointed out that testosterone may be given in selected menopausal patients for the control of a severe menopausal syndrome in those instances in which estrogens are contraindicated.

Irradiation Therapy —The use of x-ray and radium is not to be undertaken lightly in younger women because of the possibility of permanently influencing fertility and in addition diminishing the endocrine functions of the ovary. At the menopause, radium for functional bleeding is widely used and accepted, yielding results which are satisfactory in a high proportion of the cases. Serious consideration, however, should be given to patients who might not well tolerate a sudden menopausal syndrome; in some such patients a hysterectomy may be more advisable than radiotherapy. On the other hand, in the presence of such difficulties as marked obesity or other complications to surgery, this method of approach frequently affords a suitable substitute in patients in whom surgery is being considered for small myomas with associated bleeding.

In younger women, small dosages of radium or x-ray have been employed for many years as a stop-gap to control bleeding when other methods have failed in the hope that ovarian function will not be permanently effected.

In instances where the dosage has been sufficiently small, fertility may not be permanently impaired. Unfortunately it is not always possible to gauge the dosage which will produce a favorable result and yet not produce a permanent damaging effect. Also to be considered is the possibility of the effect of irradiation on the genes and the incidence of fetal abnormalities in succeeding generations if pregnancy should follow. This same problem has been raised in the use of low dosage irradiation to the pituitaries and ovaries for the treatment of functional menstrual disorders and infertility. The latter technic appears to have produced some very striking results in some cases despite the surprisingly low dosage of irradiation employed. In the main, results with this therapy appear to be best in the treatment of infertility in women with amenorrhea or oligomenorrhea. More careful study of the effects of this type of treatment upon the endocrine mechanism of the patient as well as long term follow-up of the offspring is necessary before a final evaluation can be made.

Surgery.—The place of surgical procedures other than diagnostic curettage in the treatment of functional menstrual disorders is indeed a difficult one to evaluate. In younger women the performance of a *hysterectomy* for a functional menstrual disorder which has failed to respond to medical care is an admission of defeat. Moreover, such an operation is undesirable because it permanently removes the opportunity for child-bearing. The psychologic distress and unhappiness which this may entail in the years following operation are generally better approached by the family physician than by the surgeon. On the other hand, a simple hysterectomy performed in women approaching their menopausal years may be a better answer to the problem of functional bleeding than the use of x-ray or radium in occasional delicately adjusted or nervous women in whom a sudden and severe menopausal syndrome may create difficult nervous and emotional problems.

Operations upon the ovaries in younger women is another problem requiring careful judgement. The opinion is now quite prevalent that surgery is frequently not necessary for relatively small cystic enlargements of the ovary and that conservative medical measures should be used. Certainly, repeated examination is essential in such patients since frequently ovarian enlargements are physiologic in nature, appearing at the midcycle and disappearing at a latter phase. On the other hand, the dangers of overlooking an organic lesion in a persistently enlarged ovary are not to be minimized. If surgery is performed for diagnostic purposes and a benign lesion is found, conservative management to preserve the ovary is indicated.

Presacral neurectomy to cure dysmenorrhea is a procedure not to be undertaken lightly because of the technical difficulties involved. In the hands of those most experienced with this operation a high percentage of good results has been reported. The results appear to be best in those patients who have obtained relief from pain by inhibition of ovulation, so that the latter has been suggested as a therapeutic test to aid in the choice of proper cases.

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DANGERS IN THE MANAGEMENT OF THE CLIMACTERIC

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THE climacteric is an orderly phase of the physiologic phenomenon of aging in women. The cessation of menstruation, due to ovarian inactivity, is but a part of this process. This period in women, which usually comes in the fifth decade, may be accompanied by endocrine and vasomotor instability. The climacteric is a self-limited process but the intensity, nature and duration of its symptoms vary with the individual. It should be considered a normal, orderly and progressive event and not a pathologic process.

"The hoary tradition which has been evident from time immemorial among both the laity and the profession that the menopause is an experience fraught with peril and difficulty is incorrect and unwarranted," wrote A. F. Currier in his treatise "The Menopause" published in 1897. He further stated that he was never able to see the sense nor the logic of the traditional teaching, repeated generation after generation, that the menopause was a serious—yea, even a most dangerous—time and experience and that the matron and the maid alike should approach it with fear and awe."

SYMPTOMS OF THE MENOPAUSE

The normalcy of the climacteric cannot be stressed too much. It makes its appearance usually in the fifth decade of the woman's life, its salient feature being a progressive hypo-ovarianism. The failure of ovarian function produces physiologic changes which give rise to few symptoms or may manifest themselves in a variety of symptoms. The most prominent feature is a cessation of menstruation. Not all healthy women cease menstruating in an identical manner. Occasionally the menses stop abruptly. Usually there is a progressive diminution of the flow or a lengthening of the intermenstrual interval, over a variable period of months or years until the menses finally cease. Hot flushes, which may be mild and occur only infrequently or may be severe and occur almost continuously, are characteristic. These attacks may be accompanied by perspiration and weakness. Retrogressive changes in the uterus and ovaries and external genitalia appear. The breasts show signs of atrophy.

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Other complaints at this time may be paraesthesia, hyperesthesia, headaches and vertigo, and obesity. These symptoms are not solely due to hormonal changes or estrogen deprivation, but are partly the result of the natural process of aging.

An investigation by the Medical Women's Federation of England of the climacteric history of 1000 women in whom five or more years had elapsed since the cessation of menstruation, reveals some interesting facts. Fifteen and eight-tenths per cent of the women did not have a single symptom referable to the menopause. The most frequent symptom noted was "flushes" which occurred in 62.3 per cent and varied from barely perceptible to severe. The average duration of the flushes was two years. Of these 1000 women, 89.7 per cent carried on their daily routine without a single interruption and did not absent themselves from their occupations on even one occasion because of any symptoms referable to the climacteric. Another significant finding in this study was that a patient with a normal menstrual history tends to have few symptoms at the menopause and a patient with a history of severe dysmenorrhea is more apt to have a severe menopause.

PRINCIPLES OF MANAGEMENT

The climacteric must be recognized as a phase in the inevitable and irrevocable aging process, and any therapy used at this stage must be devoted to easing the patient through this period. Most women do not require any specific therapy during the climacteric, which is self-limited in nature.

A carefully correlated history and thorough physical examination should be the first step in the treatment of women undergoing the climacteric. A meticulous search for malignant disease of the pelvic organs and breasts and other organic diseases which may be the cause of the patients' symptoms should be made.

The climacteric is a critical period in a woman's life, a time at which she finds herself to be, or rather believes that she is, entering her declining years. This patient must be aided to become mentally adjusted to her new state. Many women fear that, with the onset of the menopause, they will become less attractive sexually, and that their sex life will be disturbed. Others fear the process of aging and have heard through gossip, or have been told about the possibility of mental deterioration occurring at this time. The menopausal patient believes that the verdict of senescence has been pronounced upon her and with that verdict numerous anxieties trouble her, as for example, her place in the home, children marrying and leaving home, her loss of reproductive function, and in the single woman the threat to her economic security.

The physician must be cognizant of the fact that in advising a woman in the climacteric, he must deal primarily with a woman who is a disturbed patient and only secondarily with a person whose hormonal levels have been altered. The patient will be benefited by a simple explanation of the menopause and its significance. An attempt must be made to eliminate from her mind the many legendary misconceptions about abnormalities occurring at this time. An investigation and discussion of her personality traits, living habits, attitude toward sex, recreation and friends will be of great aid. These conferences may take time but they are more important than hormone therapy.

Perhaps a quotation from Braxton Hicks in the Croonian lectures of 1877 is in place here: 'After the change is completed the system improves, the many irritations connected with menstruation and pregnancy are gone, and the changes in the individual show that many of the earlier troubles were functional without permanent lesion. The local irritations, fluxes, and reflex symptoms—neuroses, vomiting, neuralgia and head aches—gradually pass off.'

If, after a complete check-up of the patient to rule out any organic disease and a satisfactory talk with her, she still has need of some medication to control her symptoms, one may prescribe mild sedatives. The object of therapy in the menopause should be to lower the intensity and to shorten the duration of the symptoms. Phenobarbital in suitable doses has proved of invaluable aid in alleviating most of the symptoms commonly attributed to the climacteric.

Only when the vasomotor symptoms cannot be controlled by the use of sedatives and are severe enough to become a real problem and interfere with the normal activities of the patient, should one prescribe estrogens. In prescribing estrogens one should give the smallest dose that will control the symptoms and should prescribe rest periods between courses of therapy.

When administering estrogens, the oral route is the method of choice because of its convenience and flexibility.

ERRORS AND DANGERS IN MANAGEMENT, WITH PARTICULAR REFERENCE TO THE INJUDICIOUS USE OF ESTROGEN THERAPY

The menopause has been called one of the most therapeutically abused conditions encountered in the practice of medicine (Coleman). Too often when a patient in the fifth decade of her life presents herself to her physician for advice, she is told that her symptoms are due to the 'menopause,' is treated with some hormone preparation and often is not even examined. It is too easy for the busy or undiscriminating physician to place patients at this age in the category of 'going through the

menopause" and to carry them along on "injections" or "hormone pills" without adequate investigation. The importance of the thorough examination of each patient, including laboratory tests to rule out organic disease, before she is given hormones cannot be overstressed. And of course no physical examination of a woman is complete without a pelvic examination, which must include a speculum inspection of the vagina and cervix.

Frequently the problem of irregular uterine bleeding presents itself in these patients, and a thorough investigation is necessary to determine whether the bleeding is functional or organic in origin.

The widespread and indiscriminate use of endocrine products for control of irregular uterine bleeding during the climacteric, when an organic cause remains undiscovered, has frequently led to a delay in the diagnosis of uterine cancer.

Between November 1, 1945 and January 1, 1947, the Philadelphia Committee for the Study of Pelvic Cancer investigated 455 living patients with pelvic cancer. Among these there had been a delay in diagnosis in 310. In 113 or 36.5 per cent of the latter group there was a "physician delay" in recognizing the lesion. Thirty-one of the patients whose diagnosis was subject to "physician delay" were given medication either orally or by injection without ever being subjected to a pelvic examination.

Scheffey and his co-workers state that "ill advised endocrine therapy without thorough clinical study is often an important factor in the delayed diagnosis of uterine cancer," and cite histories of such patients to support their thesis. These patients were observed in the gynecologic service of the Jefferson Medical College Hospital, Philadelphia. A typical abstract of one such case follows:

CASE I—M. V., a secundipara aged 48, admitted December 6, 1941 because of vaginal bleeding of six months' duration, had had the menopause and cessation of periods one year before, when she received a series of endocrine injections simply "for the menopause" and without internal examination. Six months prior to admission vaginal bleeding began to occur at irregular intervals. Without pelvic examination, endocrine preparations were again administered, and slight bleeding was noted almost every day. Finally a profuse vaginal hemorrhage took place and soon afterward the patient was sent to the hospital. Examination disclosed carcinoma of the cervix, group 3 (Schmitz). The histologic diagnosis was squamous cell carcinoma of the cervix, with an intermediate grade of malignancy. External irradiation was administered prior to local radium application. The patient died of carcinoma two years later.

The menopause gives the physician a rich opportunity to examine each patient thoroughly so as to discover organic disease if present. By

education of the laity to seek the advice of a physician during this period, women can be brought to the physician at periodic intervals for examination and advice. A complete examination including examination of the breasts and pelvis and laboratory tests, notably stained cervical and vaginal smears by the method of Papanicolaou, will certainly lead to the earlier detection of malignancy, not only in the pelvic organs but throughout the body.

The statistics of the Cancer Record Registry of the Connecticut State Department of Health show that the greatest incidence of malignancy of the breast and genital tract is in women between the ages of 40 and 59, and these are the ages in which the majority of women are treated for the menopause.

Not only may one err by ascribing to the menopause symptoms caused by pathological conditions of the pelvic organs, but often definite organic lesions of the other systems of the body may be overlooked by attributing the symptoms to the climacteric.

Vertigo and headache are among the most common complaints during the menopause. That there are other causes for these symptoms, however, is well illustrated by the following case.

CASE II.—L.D., a white woman aged 41, was first seen on December 2, 1946. Her chief complaints were vertigo and headaches of ten months' duration. She was a secundipara and had a normal menstrual history until age 40 when her menstrual cycle changed from a twenty-eight to a thirty-five to forty day cycle. Her symptoms of vertigo began about two months after the change in her menstrual cycle. She then (February 1946) consulted a physician who told her she was "changing" and gave her weekly injections. Her headaches continued and she consulted a second physician in October 1946 who hospitalized her, performed a dilatation and curettage and then prescribed "hormone tablets." When she was seen on December 2, 1946, her vertigo and headaches were becoming progressively worse. Her periods were occurring every thirty-five to forty days and were of normal flow. Pelvic examination was essentially normal. She was referred to a neurologist, who made a diagnosis of an aneurysm of the cerebral artery, which was confirmed at time of operation.

Gastrointestinal disturbances are also often passed over glibly when taking the history of a woman at the time of her climacteric. That serious organic lesions of the gastrointestinal tract may be missed is illustrated by the following case histories.

CASE III.—A.I., aged 39, was first seen on January 10, 1947, complaining of epigastric distress and scanty menses. She was a secundipara. Her menarche had occurred at age 11, with subsequent menses every four weeks lasting five days. The menstrual flow was liberal until March 1946 but since then her menses have

lasted only two days and are scant. Her epigastric distress dates back to January 1946. She first consulted a physician in July 1946, at which time she was told that her menopause was beginning and that this explained her gastric distress and scanty menses. She was then given injections and tablets for her menopause, over a period of six months. When seen on January 10, 1947, she complained primarily of her epigastric distress and secondarily of her scanty menses and then only because she was told that she was "menopausal." Pelvic examination revealed no gross evidence of disease. X-ray studies of her gastrointestinal tract were ordered and a diverticulum of the cardiac portion of the stomach was found.

CASE IV—H. B., aged 53, was seen February 8, 1948 complaining of nausea and flushes. She was a nullipara, with menarche at age 14 and menses every twenty-eight days, lasting three days until July 1944, when she ceased to menstruate. Nausea and flushes date back to 1945.

A physician was visited in 1946 who attributed all her symptoms to the climacteric and she was given "endocrine tablets." At the time of consultation in February 1948, pelvic examination was essentially negative and a complete gastrointestinal study was ordered. A cholecystogram showed the presence of cholelithiasis. This was confirmed at operation.

These briefly abstracted cases are not isolated instances but are used to draw attention to the fact that too often organic disease is overlooked at the time of the menopause.

"Menopausal hypertension" is a term frequently used and the climacteric has been thought of as a cause of hypertension. There is little evidence to prove this conception. Contrariwise, Taylor, Corcoran and Page, in a careful study of 200 women (ages 20 to 59) undergoing either a natural or surgical menopause, came to the conclusion "that the relationship of the menopause and hypertension is incidental and loss of ovarian secretion is neither a primary nor a contributory cause of arterial hypertension." Yet how often are hormones alone prescribed because of the finding of arterial hypertension in a woman in the fifties!

Endometriosis as a rule recedes after ovarian function ceases or at least its progress is stopped. The administration of estrogens after the menopause to patients with a history of, or suggesting endometriosis may reactivate old lesions, and thus cause a return of symptoms worse than the vasomotor phenomena of the climacteric. Faulkner and Riemen-schneider report in summary "a patient with severe periodic bleeding from endometriosis of the bowel, requiring in all over seventy partial or whole transfusions. She was finally treated by surgical castration and was well, until given diethylstilbestrol for menopausal symptoms, when severe recurrence of the bleeding took place. Permanent recovery followed discontinuance of this therapy."

The belief that the menopause induces psychiatric disorders is a rather prevalent one, and often physicians regard psychiatric complaints as an integral part of the climacteric. Here again estrogens are unnecessarily and needlessly administered to patients who are in need of psychiatric care, and thus valuable time in treatment is lost. Weaver notes that, of 2200 women who were admitted over a period of three years to the Neuropsychiatry Service of the University of Texas Hospital, over 1070 of them had received estrogenic therapy.

An intensive study of patients referred to the Department of Neuropsychiatry at the Duke University School of Medicine with the diagnosis of 'menopausal syndrome' was made by M A Greenhill. The results of his study tend to show that the majority of normal women experience no symptoms of a psychiatric nature during the menopause, and he concludes that "if a woman has never had a psychoneurosis prior to the climacterium she may expect not to have one when she experiences the involution. If a woman cannot adjust to the menopause, this is only part of repetition of a pattern of difficult adjustment throughout life."

Any patient of this age group who evinces personality disorders should have the benefit of a careful psychiatric study, so that a correct diagnosis may be reached and she may be adequately treated.

In recent years, owing to the increased use of estrogens, the occurrence of 'therapeutic bleeding' has been fairly common. The uterine bleeding produced by estrogen therapy may be due to a drop in the estrogen level after the withdrawal of the drug, or may be associated with a hyperplasia of the endometrium due to the continued use of estrogens.

That the continued ill advised administration of estrogenic substances can produce hyperplasia of the endometrium was clearly demonstrated by Novak and Yui in 1936. Recently Novak and Rutledge reported the finding of varying types and degrees of hyperplasia of the endometrium in patients who have been on prolonged courses of estrogen therapy. In some instances, the proliferative activity was so great that it could easily be mistaken for carcinomatous changes. Gusberg in his study of uterine bleeding following hormonal medication also noted that advanced degrees of endometrial hyperplasia can be produced by the prolonged use of estrogens. That the proliferative forces responsible for the endometrial hyperplasia may also predispose to the development of endometrial carcinoma is not without reason. Novak and Yui in a study of 104 cases of fundal carcinoma found a coexisting hyperplasia in 24 per cent.

The high incidence of corpus carcinoma associated with granulosa cell tumors of the ovary seems to be more than coincidental. Hodgson, Dockerty and Mussey reported 21 per cent of thirty-eight postmeno-

pausal patients with granulosa cell tumors to have an associated carcinoma of the fundus Smith reported finding endometrial carcinoma coexistent with granulosa cell tumors in 15 to 20 per cent of his cases of the latter Here the effect of the excessive stimulation of the endometrium by an abnormal source of endogenous estrogens must be reckoned with

The association of a delayed menopause and fundal malignancy has also been studied in some detail This poses the question of the relation of prolonged estrogenic activity, as indicated by the delayed menopause, and fundal malignancy Crossen and Hobbs found that in 60 per cent of cases of fundal carcinoma the patients had menstruated to the age of 50 years in contrast to 15 per cent in the normal cases Randall states that the woman with a history of menorrhagia during the climacteric has three and one-half times greater chance of developing cancer than the woman who had no increased bleeding prior to the cessation of her periods May not the administration of estrogens over a long period of time be prolonging the menopause, and thereby bring into action forces that may prove dangerous to the individual?

As a rule, estrogen therapy is directed to simulate the normal course of events In giving it do we not at times go contrariwise to normal physiology? Estrogens may prolong the period of normal adjustment of the individual to her changed hormonal status Thus, an individual who has been on estrogenic therapy needlessly, may at the cessation of therapy be totally unadjusted again One must conclude that the prescribing of estrogens for an indefinite period of time is dangerous One should remember that, normally, the patient establishes a hormonal equilibrium and her symptoms disappear spontaneously

There is enough evidence on hand that prolonged estrogen therapy may produce endometrial hyperplasia Though there is no positive evidence of the incitement of malignancy by estrogenic therapy, the case report by Fremont-Smith, Meigs, Graham and Gilbert, of the occurrence of endometrial cancer in a woman undergoing prolonged treatment with estrogen and who had been under observation for eighteen years and had had previous negative curettages, certainly casts some suspicion on the estrogen therapy

The data presented by Gusberg in five patients who developed adenocarcinoma of the fundus following prolonged estrogen administration is also significant Uterine bleeding in a woman receiving estrogen therapy should always be investigated Only a diagnostic curettage can rule out the presence of malignancy Once a patient shows signs of bleeding following estrogen therapy, she should never be given such therapy again In a few selected cases, one may control her vasomotor symptoms, if they are a problem, by the administration of androgens suitably supervised

Patients who have received x ray or radium therapy for abnormal bleeding should never be given estrogens at a later date. Certainly, one should never prescribe estrogens for patients who have been treated for pelvic malignancy.

Women who give a history of the occurrence of malignancy in the family, or who themselves have had benign neoplasms in the past, certainly should not be subjected to prolonged estrogen therapy. Here again androgens may be of some value if conservative sedative therapy fails to alleviate her symptoms.

The dangers incident to the ill advised and indiscriminate use of estrogens in the climacteric do not condemn them absolutely, and should not cause one to deprive oneself of a sometimes valuable aid in the control of symptoms incident to the menopause, in carefully selected cases.

In managing women in the climacteric, it would be well to bear in mind Skene's observation in 1888. A long list of diseases has been given as occurring at the menopause. This list covers all the ills the flesh is heir to. The majority of these have no relation to the menopause, the menopause only determining the time of their development.

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NEWER APPROACHES IN FERTILITY STUDIES

S LEON ISRAEL, M D , I A C S *

THE basic force in the sustained adventure of a happy marriage is the presence of children. The childless marriage may become an unhappy misadventure because the partners have no opportunity to subordinate themselves as parents. Since it may result in deep marital unhappiness, the barren marriage is a constant source of concern to society. Its exact incidence is difficult to compute. According to present day estimates, approximately 17 per cent of all married women never bear any children.¹ However, some of this childlessness is voluntary. The estimated occurrence of involuntary sterility is approximately one in every eight marriages, or about 13 per cent.² According to Meeker, there are generally two million involuntarily childless couples in the United States at all times.³

The mere frequency of the barren marriage, to say nothing of its major social implications, makes it a dynamic medical problem.

CLASSIFICATION OF STERILITY

Recent studies of sterility rates have emphasized that the earlier definitions of primary and of secondary sterility are too conservative. Despite the obvious fact that many variables, such as coital rates and physiologic barriers, affect the general rate of conception, a year's trial is an adequate standard. The figures of Stix and Notestein⁴ and of Russell⁵ indicate that two-thirds of pregnancies occur within three months of the initiation of unprotected coitus. Diddle and his co-workers conclude, from a survey of 318 pregnant, married, white women, that 86 per cent of primigravidas and 65 per cent of multigravidas conceive within the first year of using no contraception.⁶ In a study of 500 planned pregnancies, Stone observed that 80 per cent had been achieved within six months of discontinuing contraception.⁷ These data indicate that the customary insistence upon two years of unprotected coitus before considering a childless couple barren is a standard exaggerated beyond the fact.

Primary sterility should be considered present when conception has not occurred after one year of continuous marital life without the use of contraception. Rubin, distressed by the frequency with which the use of contraceptives masks sterility, recommends that persons contemplating

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marriage consult a physician regarding their capability for reproduction, or do so soon after marriage.⁸ Such a practice would avoid both the unnecessary contraceptive measures and the loss of precious time in identifying the 15 per cent of sterile matings.

Secondary sterility should be considered present when a woman who had previously borne one or more children is not pregnant after two years' continuous trial. This longer period of attempted conception is permissible for a parous individual because of the physiologic sterility which occurs for several months after delivery as a result of anovulation.^{9, 10}

For purposes of investigation, as well as in the interest of attaining good results, the etiology of primary and secondary sterility is considered identical.

ETIOLOGY OF STERILITY

The causes of barrenness, though multiple and complex, are easily classified because the mechanism of conception is, after all, relatively simple. The essential factors controlling fertility are:

- 1 The more or less cyclic production of a normal ovum which must enter a fallopian tube for fertilization and then be transported to a prepared site of implantation in the endometrium.
- 2 The repeated availability of a large number of normal spermatozoa in a favorable, transportable medium.
- 3 The timely insemination of the mucus-laden cervix and the ascent of the spermatozoa through the uterine cavity, enabling fertilization of the ovum in the tube.

A mere perusal of these factors serves to emphasize the culpability of both marital partners in the etiology of sterility. The burden of responsibility may no longer be placed solely upon the wife who, seeking to satisfy her innate desire for motherhood, is usually the one to enlist medical aid and to submit freely to investigative procedures. A sterile union does not arise from defects in only one partner but is rather the result of the sum total of several factors, often minor, in both partners. In carefully analyzed series, the incidence of multiple causes of sterility in each partner may be as high as 60 per cent.¹¹ Appreciation of this fact is, in large measure, responsible for the current betterment of therapeutic results.

The physician who undertakes the care of a barren couple must subscribe fully to this modern concept of the multiple causation of sterility and must pursue a fixed plan of study. Such a plan "includes an orderly, systematic history of the sterile couple, an unremitting search for multiple etiologic factors in each partner, and persistence in eliminating *all* possible impediments to conception, regardless of how minor they may

seem to appear.' The barren couple must, on the other hand, be willing to submit to the search for etiologic factors, the pursuit of which takes both time and patience. The required cooperation is easy to obtain if the physician orients the couple initially on the need for an adequate diagnostic evaluation.

The first visit of the wife, or of the couple, to the physician is the time for explanation of the likelihood of multiple etiologic faults and for presentation of the plan of investigation. An estimate of the husband's interest in the problem lies within the province of this initial discussion. There is no justification for the ungracious attitude of the recalcitrant husband whose lofty masculine ego bristles with indignation at the merest question of his reproductive ability. The physician, as well as the wife, must insist upon complete cooperation of the husband from the outset, refusing to initiate diagnostic studies without it. Finally, it should be established at this first visit that no active treatment will be undertaken without strict adherence to the entire diagnostic program. Empiric short-cuts to haphazard therapy in the hope of a chance pregnancy, usually result in loss of the couple's precious time, a waste of their financial resources, and in their eventual disillusionment.

In view of the frequently protracted character of the investigation, expensive studies of purely academic interest should be kept to a minimum. Moreover, the various fees should be flexible, adjusted to the couple's economic status.

MINIMAL DIAGNOSTIC SURVEY

The systematic investigation of a barren couple is not so formidable a ritual as to discourage the interested family physician. He may certainly plan and, in some measure, execute the searching formula. A few of the studies do require particular facilities and special skills, but such examinations may be performed either by consulting specialists or in diagnostic clinics.

An exacting history of each partner's medical background is valuable in the initial estimate of the situation, for it may provide important clues. Medical interrogation of the couple to obtain such a history is admittedly time-consuming. The use of an all inclusive confidential questionnaire, answered by the couple and analyzed by the physician, results in a detailed history with a minimum expenditure of time. A good infertility questionnaire is that of Weisman.¹²

Bearing in mind the physiology of conception and the probability of multiple causes for its dysfunction, the physician should seek to uncover the following essential etiologic factors:

I. *Male infertility* which finds expression clinically in faults of the

semen It is present, in various degrees, in nearly 50 per cent of the husbands studied

II *Gross pelvic disease*, such as tumors and infections, conditions inimical to the initiation and maintenance of gestation Such abnormalities are usually delineated by a carefully performed gynecologic examination The incidence of this factor is about 5 per cent

III *Errors of cervical insemination* which include failure to deposit the semen properly, defective invasion of the cervical canal by spermatozoa, and hostility of the cervical secretion It is evaluated by an examination of the postcoital cervical and vaginal secretions, and is found in about 25 per cent of barren couples

IV *Tubal occlusion*, partial or complete, recognizable either by means of insufflation (the Rubin test) or by radiography (uterosalpingography) The fallopian tubes are at fault in about 50 per cent of the wives studied

V *Endocrine faults in the female* which include temporal abnormalities of menstruation and anovulation These exist in about 25 per cent of barren women

The sequential order of conducting the study should, of course, be flexible, varying with the availability of the marital partners and with the menstrual cycle However, it is advantageous to evaluate the male factor early in the course of the investigation

I MALE INFERTILITY

Fertility in the male depends on adequate development of the genital organs and proper function of the endocrine system The maintenance of fertility is vested in the anterior lobe of the pituitary and the testes They are, however, influenced by the functional activity of other endocrine glands, as well as by certain mechanical, nutritional, and toxic factors The clinical approach to the diagnosis of male infertility must, therefore, systematically consider the etiologic possibilities of adiposogenital dystrophy (Frohlich's syndrome), primary hypogonadism (eunuchoidism), malfunction of the thyroid gland, malnutrition, genital infection, disturbances of testicular circulation, cryptorchidism, and recurrent physical exposure to radiation The occupational hazard of accidental sterilization among radiologic workers is real Hickey and Hall¹³ report a 37 per cent incidence of sterility in 377 circularized radiologists

The *history* of the husband should be thoroughly elicited, with special emphasis on any genitourinary difficulties and in regard to sexual habits The latter need not conform to any particular pattern It is important, however, that the frequency of coitus is such that it is likely to occur during the probable time of the wife's ovulation On the other hand, it should not be so often as once daily during that period because fertility

is thereby adversely affected. Repeated ejaculation at intervals of less than twenty four hours causes a reduction of the number of spermatozoa,¹⁴ as well as an increase in the number of abnormal forms.¹⁵

The physical examination of the husband should be performed by one sufficiently familiar with male anatomy so that endocrine stigmata, abnormalities of the penis and testes, palpable changes of the genital adnexa, and alterations of the prostatic and seminal vesicular secretions will be recognized. Routine laboratory procedures such as urinalysis, blood count and serology should be part of the initial physical examination. However, special studies such as endocrine bio-assay and sugar tolerance test should be postponed until the need for them is crystallized by the semen examination and, if indicated, by a testicular biopsy.

TABLE 1
BASIC FACTORS TO BE CONSIDERED IN THE FERTILITY APPRAISAL OF SEMEN

| Factors | Values in Fertile Men* | |
|---------------------------------|------------------------|----------------|
| | Average Range | Median Average |
| 1 Volume | 2 to 6 cc. | 4 cc. |
| 2 Number of spermatozoa per cc. | 60 to 150 million | 100 million |
| 3 Percentage of normal forms | 70% to 90% | 80% |
| 4 Percentage motile | 40% to 90% | 50% |

* Each of these numerical values does not mark a boundary between fertility and sterility. Male fertility is the product of all four factors. Thus, a slight deficiency of one characteristic may be compensated by an overabundance of another.

Examination of the Semen—A competent appraisal of the semen early in the minimal diagnostic survey enables one to evaluate properly the degree of male responsibility and, if necessary, to begin treatment.

The importance of the method of semen collection cannot be overestimated because some abnormal findings in the semen arise from an improper technic of either collection or transmission of the specimen. The semen should be obtained, after several days abstinence, either by withdrawal during unprotected coitus or by masturbation. Ejaculation should occur directly into a dry, widemouthed, glass vial, care being exercised to collect the initial portion of the ejaculate and to avoid contamination by any type of lubricant. It should be transmitted for examination at ordinary temperature, preferably within two hours of its collection.

The examination of the semen should be complete, reflecting the factors summarized in Table 1. Detailed descriptions of the various investigative procedures applicable to the semen may be found in recent publications devoted to the subject.^{14 16 17}

Current research in the enzymatic chemistry, metabolism and fertilizing capacity of spermatozoa may result in a better understanding of the factors which control spermatozoal motility^{18, 19}. Inasmuch as motility is the only criterion for determining viability of spermatozoa, such studies bear directly on the therapeutic problem created by the individual with an adequate number of morphologically perfect, but immotile, spermatozoa.

Another question of equal importance is the relation of the enzyme, hyaluronidase, to the mechanism of fertilization. This substance, al-

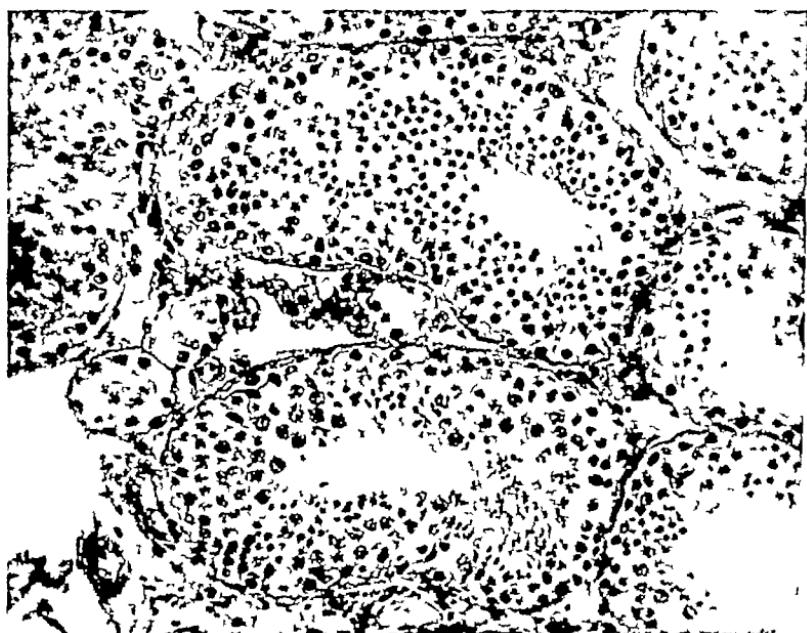


Fig 183.—Testicular biopsy, showing cross section of normal seminiferous tubules
X 250 (Courtesy of Dr Charles W Charny)

legedly adsorbed on the surface of the spermatozoon, is supposed to cause dispersion of the follicle cells, the cumulus, surrounding the recently ovulated ovum. If this is true in man, the purpose of the large number of spermatozoa required per ejaculate to insure the entrance of one into the ovum may well be "the production of a concentration of hyaluronidase sufficient to liquefy the hyaluronic acid gel" in which the cells of the cumulus are embedded.²⁰ However, until more is known of the origin of hyaluronidase in semen, whether it is the product of living or dead spermatozoa,²¹ assays for its presence and its clinical usage should be regarded as experimental.²²

Testicular Biopsy.—The study of tissue obtained by biopsy of the

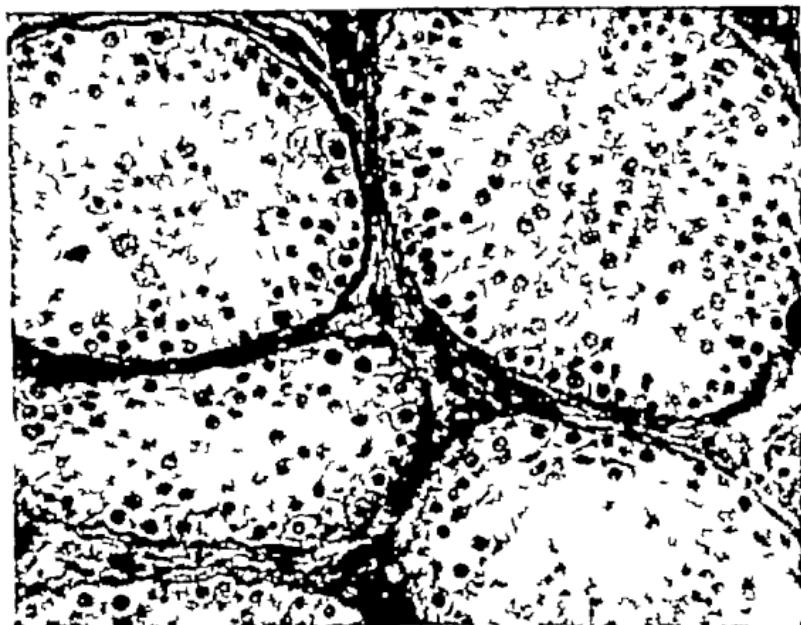


Fig. 184.—Testicular biopsy showing degenerative lesion of seminiferous tubules and exfoliation of incompletely matured seminal epithelium. $\times 250$ (Courtesy of Dr. Charles W. Charny.)



Fig. 185.—Testicular biopsy showing complete atrophy of seminal epithelium. Note survival of Sertoli cells. $\times 250$ (Courtesy of Dr. Charles W. Charny.)

testes, a simple procedure requiring no special skill and entailing no incapacitation,¹⁴ is a reliable method of differentiating the causes of seminal deficiencies. The clinical usefulness of a careful microscopic study is apparent from the definite information it yields concerning the presence or absence of normal germinal epithelium. If the oligo- or azoospermia is caused by an occlusion of the seminal tract, the biopsy will show well-constructed seminiferous tubules. If the seminal deficiency is the result of defective germinal tissue, the degree of involvement and the probable regenerative capacity of the tubular epithelium may be observed.²³ Testicular biopsy allows prognostication, aids the selection of proper treatment of azoospermia caused by faulty transmission, and enables the avoidance of useless therapy, for complete degeneration of the seminiferous tubules defies present-day methods (Figs 183-185).

II GROSS PELVIC DISEASE

The finding of a gross pelvic abnormality during the initial gynecologic examination suspends further investigation of the barrenness until the disorder in question is evaluated. The largest number of such grossly palpable conditions, accidentally uncovered in the preliminary survey of a woman whose complaint is sterility, are of inflammatory origin. However, myomas and congenital malformations of the uterus, as well as tumors of the ovary, are also encountered.

Pelvic Inflammation —The most frequent cause of infertility in women is either gonococcic or pyogenic inflammatory disease which results in tubal occlusion and chronic endocervicitis. These residua, not usually grossly palpable, are recognized in other ways. The presence, however, of a large hydro- or pyosalpinx precludes further gynecologic study and impels the use of antibiotics, pelvic rest, and local heat. If such therapy does not cause resolution of the adnexal masses, conservative and reconstructive surgical treatment should be applied.

Occult, subclinical *tuberculosis* of the female genital organs is not easily recognized by bimanual palpation. It should, nevertheless, be suspected in any sterile woman presenting palpable adnexitis who has a history of pleurisy, cervical adenitis, or of hip disease during girlhood, or who carries the scars of a pararectal fistula. If the diagnosis is established by the finding of tubercles in the endometrium obtained by curettage, the minimal diagnostic survey should be relinquished to the treatment for tuberculosis.

Myomas of the Uterus —Any tumor of the uterus large enough to evoke symptoms by pressure of neighboring organs requires surgical treatment. The etiologic importance, however, of smaller myomas depends upon their size and location. Uterosalpingography must be em-

ployed to discover whether the palpable tumors hinder fertility either by grossly distorting the endometrial surface or by occluding the interstitial portion of the fallopian tubes. In the sterile woman, myomectomy is, obviously, the procedure of election whenever surgical treatment is to be employed. If there is no other cause of barrenness, 38 per cent of sterile women may be expected to conceive following abdominal myomectomy.²⁴



Fig. 186.—Roentgenogram, demonstrating double uterus by means of two sounds.

Malformations of the Uterus.—Various degrees of failure of the müllerian ducts to fuse may result in either palpable or visible abnormalities of the uterus.

If the extent of the malformation is not determined by the initial pelvic examination, radiographic study is indicated. Such an investigation of a suspected double cervical canal may lead to the proper diagnosis of a palpable uterine tumor previously considered to be a subserous myoma (Figs. 186, 187).

The finding of congenital retroversion of the uterus, not the fixed malposition resulting from pelvic inflammation, should not delay the progress of the minimal diagnostic survey. If subsequent study proves the malposition to interfere with insemination of the cervix, it may be corrected bimanually and held in normal position by a Smith Hodge pessary.

until pregnancy occurs. Surgical treatment is rarely indicated for this type of correctible malposition.

Tumors of the Ovary — Grossly recognizable cystadenoma of an ovary, without symptoms other than involuntary barrenness, is occasionally encountered. In some patients, the associated amenorrhea often mimics pregnancy, requiring a biologic test. The removal of a gross ovarian tumor in a barren woman supersedes the study of her sterility. If it is large enough to warrant removal, cystectomy is the treatment of choice.²⁴



Fig 187.—Uterosalpingogram of double uterus.

Ovaries containing retention cysts, palpable bimanually as slightly enlarged, irregularly shaped organs, are usually harmless except when associated with amenorrhea and sterility. When such cystic ovaries are the only discernible cause of sterility, wedge-shaped cortical resection of both ovaries is justifiable.²⁵

III ERRORS OF CERVICAL INSEMINATION

Penetration of the cervical mucus by a large number of spermatozoa is essential to fertility. This necessitates both the proper deposition of normal semen and a salutary state of the cervical canal. The microscopic

study of the postcoital cervical and vaginal secretions, the Sims-Huhner test, provides the means to determine these factors. However, such a test is no substitute for a careful examination of the semen. The availability of adequate spermatozoa should be known before attempting to assay errors of cervical insemination. Moreover, the cyclic physiology of the cervix must be considered and the test performed at the time when spermatozoa are intended to penetrate the cervical mucus easily, at ovulation.²⁶

Timing and Technic of Sims Huhner Test.—Cervical mucus is most readily penetrable by spermatozoa during the midportion of the cycle, coinciding with the ovulatory dip of the basal body temperature curve (Fig. 191). At this time, the cervical mucus is most abundant, possesses its lowest viscosity and cellularity, has a high content of water, and is well supplied with glycogen.^{27 28 29} The test is most reliable, therefore, when it is timed to coincide with the period of expected ovulation.

Practical experience has emphasized the importance of not prescribing a definite day for the test. It is better to suggest that the couple select one of several days approximating ovulation, after two days of sexual abstinence. This avoids the psychogenic impotence often occasioned in the husband by appointed intercourse. The wife is directed to report for examination within five hours of the elective coitus, being certain to avoid, in the interim, douching and bathing.

To obtain the secretions, the patient is placed in the usual gynecologic position and the cervix exposed by means of a dry, nonlubricated bivalve speculum. The vaginal pool is aspirated by means of one dry, sterile pipette, and the cervical canal by another. Each specimen is placed on a glass slide, topped with a cover slip, and examined microscopically.

Interpretation of the Sims Huhner Test.—The evaluation of the postcoital test presumes the presence of normal semen. When collected within five hours of intercourse, the vaginal specimen should show a considerable number of nonmotile and the cervical secretion approximately 15 actively motile spermatozoa per high power field. If the findings do not conform to the expected normal, the test should be repeated. No conclusions should be drawn from a single test. The following variations, *presuming the presence of normal semen*, may be encountered:

1. The repeated absence of spermatozoa in both the vaginal pool and the cervical secretion implies faulty coital technic.

2. The repeated presence of inactive spermatozoa in the cervical secretion is indicative of cervical hostility, usually of inflammatory origin (chronic cervicitis) but occasionally endocrine in nature (ovarian deficiency). The associated finding of an uncountable number of leukocytes in the cervical secretion is presumptive evidence of endocervicitis.

3 The repeated absence of spermatozoa in the cervical canal and their simultaneous presence in the vaginal secretion may be caused by a viscid endocervical plug, a cervical polyp, the absence of proper cervical mucus (wrong day of cycle), and, rarely, by an anterior position of the cervix

IV TUBAL OCCLUSION

Fertility depends on the presence of patent and normally contractile fallopian tubes Bilateral tubal occlusion, partial or complete, is usually the result of a preceding gonococcal or postabortal infection Occasionally, loss of peristalsis is the only residuum of such salpingitis Rarely, as mentioned previously, asymptomatic genital tuberculosis is the basis for tubal dysfunction An evaluation of tubal function is indispensable in the study of sterility It may be established either by uterotubal insufflation with carbon dioxide (Rubin test) or by uterosalpingography These two diagnostic methods are not in competition, for each has advantages under varied circumstances The Rubin test is more commonly employed because it is simple and expedient, being possible of execution "anywhere by a single individual" Moreover, if the tubes are shown to be normally patent, it makes further tubal study unnecessary Utersalpingography, most commonly used to evaluate the abnormal results of several Rubin tests, requires radiographic technic Weisman, employing a new apparatus (gynograph), combines both procedures in a single examination³⁰ The two methods are safe if proper precautions are observed

Contraindications to Uterotubal Insufflation and Utersalpingography—The untoward complications which occasionally follow tubal studies may generally be traced either to poor timing or to carelessness in selection of the patient To avoid unfavorable reactions, the following conditions must be regarded as strict deterrents to the use of tubal diagnostic methods

1 The presence of acute or chronic pelvic disease, including chronic cervicitis and *Trichomonas vaginalis* vaginitis It is obvious that each procedure may cause an exacerbation of chronic pelvic inflammation A pelvic examination should immediately precede the tubal study to delineate the presence of smoldering salpingitis and of chronic endocervicitis If any suspicion of genital infection exists, the study should be postponed Infected cervical erosions should be cauterized and permitted to heal first

2 An imminent menstrual flow or the presence of uterine bleeding The most favorable time for testing tubal patency is, as indicated by Rubin,³¹ between the fourth and seventh day following the cessation of a normal menstrual flow This avoids interference with a chance pregnancy, eliminates the danger of embolism through the entrance of gas or opaque

medium into open uterine blood vessels, and precludes a false interpretation of occlusion because of the lush, premenstrual endometrium. In irregularly menstruating women, the examination should be performed not later than five days after the cessation of a flow unless a biologic test excludes an early pregnancy.

- 3 Any systemic disorder which renders conception undesirable
- 4 An interval of less than a month after any intrauterine manipulation. This is a safeguard against the spread of infection
- 5 A history of temperature and abdominal pain following a previous Rubin test. This suggests the existence of quiescent tuberculous salpingitis and motivates a careful search for a pulmonary lesion.

Technic of the Rubin Test—The patient is placed in the lithotomy position. Preliminary pelvic examination is necessary to determine the presence of any local contraindication and to ascertain the position of the uterus. The cervix is exposed by means of a bivalve speculum, cleansed, and antisepticized. A sound is passed gently through the cervical canal to determine its direction and degree of resistance. A sterile Keyes Ultzmann cannula, having first been connected by rubber tubing to the source of carbon dioxide and having been tested for patency, is now passed into the uterine cavity. An air tight connection must be maintained between the external os and the collar of the cannula. This frequently, but not always, requires traction on the cervix by means of a tenaculum. To avoid uterotubal spasm, it is best not to allow the gas to flow until the cannula has been in the uterine cavity for approximately two minutes. The gas should then be permitted to flow under volumetric and manometric control—90 cc per minute at a pressure of from 10 to 15 pounds. The pressure recorded as the gas flows through the uterus and tubes should not be permitted to exceed 200 mm of mercury. If a negative test is obtained, it should be repeated several times during the initial session to be certain that tubal spasm is not the cause.

The kymographic type of apparatus affords a permanent, visual record and is by far the most accurate type (Fig. 188). However, there is no real objection to a nonrecording apparatus if carbon dioxide is employed under controlled pressure. The disadvantages of the hand bulb-air method include the lack of accuracy, the difficulty in recognizing tubal peristalsis, and an increase in pain because of the slower absorption of nitrogen.

The interpretation of the Rubin test depends on the pressure levels recorded or observed, and the type of pain experienced by the patient during the test, as well as on the presence or absence of shoulder pain following the procedure. The degree of abdominal pain varies with the sensitivity of the patient, but cramps, similar to those present at the onset

of menstruation, are experienced by most during the test. Severe pain, especially when unilateral, is the result of distention of a tube occluded at the fimbriated end. When the patient assumes a sitting position, the physician should expect to be told of the transitory shoulder pain if sufficient gas entered the peritoneal cavity through the patent tubes. This pain—usually right-sided, occasionally bilateral—is pathognomonic of some degree of tubal patency. Tubes that permit the passage of only 30 cc of carbon dioxide per minute at a pressure of 80 mm of mercury, or transmit the customary 90 cc per minute at the high pressure of 200 mm of mercury, are definitely strictured. Shoulder pain will occur in both instances if at least 200 cc of gas are passed.

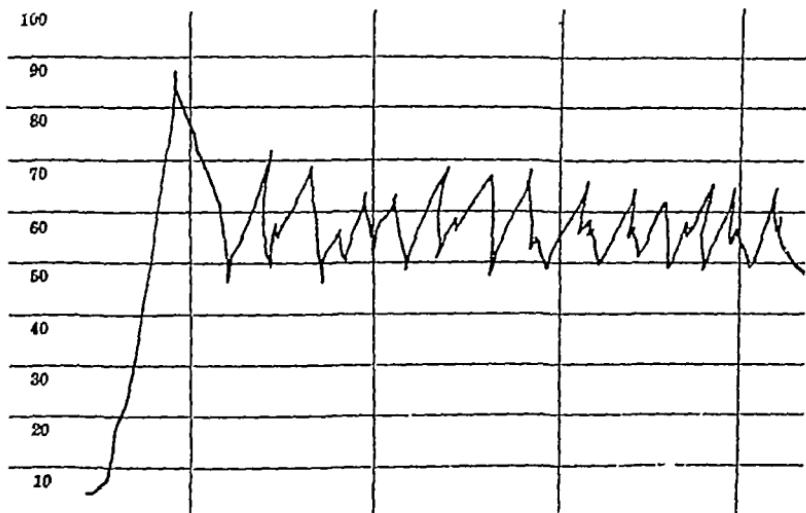


Fig. 188.—Kymographic record of normal uterotubal insufflation (Rubin test).
Note peristaltic waves

Confirmatory evidence of tubal patency is derived from auscultation of the lower abdomen during the test. The bubbling of the gas through normal tubes is audible as a low-pitched, intermittent sound. It is high-pitched and continuous if the tubes are stenotic.

Uterosalpingography—Although uterosalpingography is an alternate method of determining tubal patency, it does not supplant the simpler, less costly Rubin test. It is usually employed to locate the site of obstruction when salpingoplasty is contemplated, to study the intrauterine contour for suspected neoplasm, and as an empiric therapeutic measure.

The *apparatus* required for uterosalpingography consists of a syringe attached either to a Keyes-Ultzmann or to a screw-type, self-retaining cannula.³⁹ The Jarchó pressometer, allowing control of the pressure employed during the intrauterine instillation of the opaque medium, may



Fig. 189.—Uterosalpingogram employing rapidly absorbable contrast medium. Note narrow lumen of normally patent tubes.

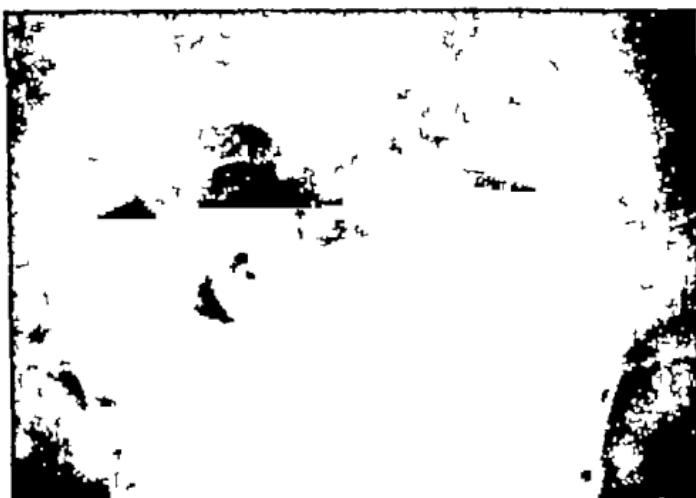


Fig. 190.—Uterosalpingogram, made with soluble medium showing occlusion of isthmic portion of left tube.

be incorporated into the system with advantage.³³ The procedure is most informative when it is performed fluoroscopically, a technic which permits observation of the flowing solution and enables the taking of selected serial films. Intrauterine lesions are best detected by the negative shadows observed as the uterine cavity is filled.

The *radiopaque media* available for uterosalpingography are legion, consisting either of solutions of iodine in oil, or of water-soluble, chemical combinations of iodine salts. The oily substances afford excellent contrast media but are associated with the highest incidence of untoward reactions. The aqueous solutions, although combined with viscous agents, are too rapidly absorbed to permit visualization of the delayed emptying of the tubes, a finding characteristic of partial occlusion. The author now employs Rayopake,* a water-soluble substance introduced by Rubin³⁴ and adequately tested by others.^{35 36} It is as viscous as an oily solution, causes no observable chemical irritation, and gives clarity of contrast (Figs. 189, 190).

V ENDOCRINE FAULTS IN THE FEMALE

The complete dependence of reproduction on the integrity of the endocrine system is an accepted fact. From the standpoint of fertility, normal menstruation—rhythmic dismantling of an estrogen-primed and progestin-modified endometrium—as determined by premenstrual biopsy or curettage, connotes an intact endocrine system. Deviations from the normal point to disruption of the pituitary-ovarian-uterine mechanism. From the standpoint of diagnosis, the endocrine factors in the female partner may be divided into two groups: (1) abnormalities of menstrual rhythm, namely, amenorrhea and dysfunctional uterine bleeding, and (2) anovular menstruation.

Dysfunctional menstrual disorders, amenorrhea and abnormal bleeding, are obvious handmaidens to sterility. Their presence permits the assumption that an endocrine fault in the female exists and should impel the execution of diagnostic surveys which will lead to their correction. (The management of menstrual aberrations is not germane to this review, but may be found in detail elsewhere.¹¹) Anovular menstruation, however, is clinically indistinguishable from normal menstruation and its presence must be excluded in every barren woman by some proof of cyclic ovulation. Such anovulatory bleeding may be outwardly identical with ovulatory menstrual bleeding but it occurs from an endometrium

* Rayopake (Roche) is a viscous, aqueous solution, possessing an iodine content of approximately 15 per cent.

totally lacking a secretory pattern, usually because of the lack of both ovulation and luteinization.

Anovulatory cycles are physiologic in puberal girls, as well as in lactating and premenopausal women. They occur occasionally in all regularly menstruating women and assume importance only in the presence of barrenness. Estimates of the incidence of regular anovulatory menstruation among sterile women vary from 5 to 15 per cent, depending on the criteria employed for its recognition. However, its frequency is greater in those in whom no other cause of sterility exists.¹⁷ The diagnosis of regular anovulation should be established by repeated observations because the occurrence of an occasional anovulatory cycle may, as indicated previously, be physiologic. Finally, when it is recognized the prognosis for conception—in view of present-day therapy for it—should be guarded.

The *diagnosis* of anovulatory menstruation as an etiologic factor in sterility rests on repeated demonstration of the failure of ovulation. Inasmuch as the ovaries cannot be inspected during each menstrual cycle, the physician must select other criteria which reflect ovarian function. Moreover, if such diagnostic methods are to be employed on a wide scale, they must be simple. Laboratory procedures which entail repeated biologic assays are not practical for average use. Currently, the most expedient method of repeatedly observing ovarian function is the graphic recording of the daily body temperature. If anovulation is demonstrated by the temperature chart, further investigation of the degree of ovarian failure is indicated. It is then advisable to employ such methods as endometrial biopsy, repeated study of vaginal smears, and assays for pituitary gonadotrophin.

Basal Body Temperature —The biphasic fluctuation of body temperature in association with the menstrual cycle, observed in 1904 by Van de Velde and popularized more recently by Rubenstein²³ and Zuck,²⁴ has been correlated as a sign of ovulation in a most convincing manner.²⁵⁻⁴⁴ The body temperature of a normal woman is not constant but follows a rather fixed pattern during the menstrual cycle (Fig. 101). During the estrogen phase, the temperature is relatively low, varying from one-tenth to three-tenths of a degree daily. The lowest point is reached just before ovulation, following which a characteristic rise of more than one-half degree occurs. During the luteal phase the temperature is relatively high, remaining—despite slight daily variations—noticeably above the level maintained during the pre-ovulatory portion of the cycle. The temperature drops with the regression of the corpus luteum, about two days prior to menstruation. If pregnancy ensues, the temperature remains at the luteal level (Fig. 102).

The recording of the temperature must be done with the utmost care because the variation between the pre- and the postovulatory levels is small (0.1 to 0.3°F). The following practical rules are helpful:

- 1 Be certain that the patient knows how to read a thermometer
 - 2 Advise the use of a rectal thermometer because there is less likelihood of false variation from extraneous causes
 - 3 Instruct the patient to take her temperature every morning at the time of waking, before she gets out of bed for any purpose, and to record

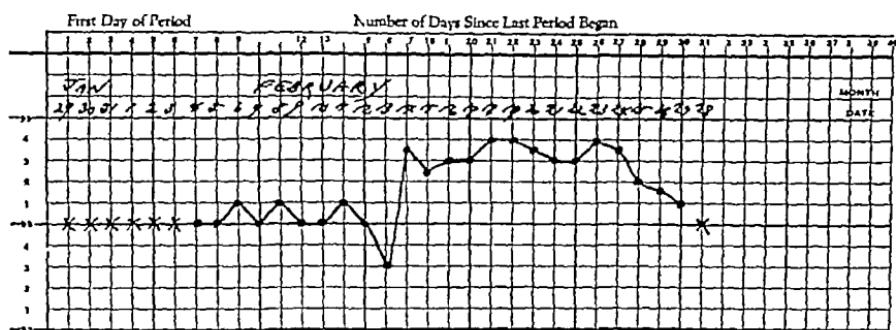


Fig 191—Body temperature graph, illustrating ovulatory dip and rise Note obvious biphasic character of record Menstruation denoted by x

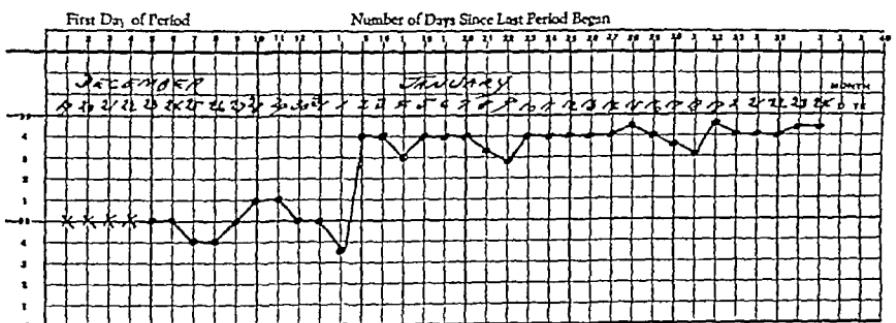


Fig. 192.—Body temperature graph of early pregnancy, showing persistence of elevation.

the reading immediately. The reading should not be made until the thermometer has been held in the rectum for five minutes.

- 4 Have the patient keep a simple graph of the daily readings if she is adept at such things, if not, have her bring the recorded figures to the physician's office for construction of the graph *

- 5 Direct the patient to record, in addition to the daily temperature,

* Charts for this purpose may be obtained from the Planned Parenthood Federation of America, Inc., the American Association for the Study of Sterility, and from one of several pharmaceutical companies.

the days of menstruation and any occurrence which might affect temperature-readings (infections, insomnia, etc.)

The interpretation of the temperature graph must be made with a view to its limitations. Being an index of a delicate physiologic process, it is not infallible. When the temperature record is clearcut, the pre-ovulatory dip and the ovulatory rise being sharply delineated (Fig. 101), there is no difficulty in timing ovulation. On the other hand, the absence of a sharp low point in association with a slight but persistent rise and the curve with a gradual gradient are features which hinder decisive recognition of ovulation. The gradual, slow rising graph (Fig. 103) is particularly baffling. Its biphasic character suggests the occurrence of ovulation but does not allow selection of the day it occurred. It is currently thought that such a curve is the result of either pre-ovulatory luteinization of the

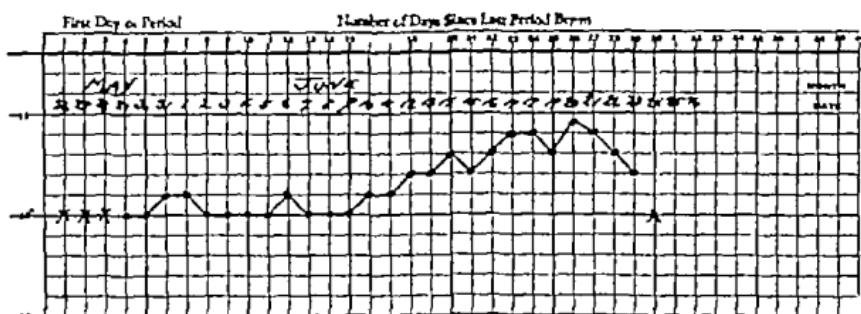


Fig. 103.—Atypical biphasic curve of body temperature graph. Note absence of ovulatory dip and of acute rise.

follicle or delayed development of the corpus luteum. It is as if the hypothermic force (estrogen) and the hyperthermic factor (progesterone) were struggling for dominance.

When ovulatory cycles are repeatedly evident from the temperature graphs, it may be assumed that no endocrine factor exists in that patient—at least, insofar as the production and release of ova are concerned. There is no means, unfortunately, of recognizing either the ability of the free ovum to be fertilized or its subsequent developmental capabilities. However, when indecisive temperatures make it impossible to determine the frequency of anovulatory cycles, a correlated evaluation should be attempted by means of endometrial biopsy.

Biopsy of the Endometrium—The histology of the premenstrual endometrium provides reliable information concerning the occurrence of ovulation, the formation of a functioning corpus luteum, and the endometrial responsiveness to the ovarian steroids. The endometrial specimen, obtained by either biopsy or curettage, is most trustworthy when

it is procured several days prior to the expected flow, before the regressive changes immediately preceding menstruation have taken place. The latter prevent accurate interpretation.¹¹⁻⁴⁵ Many gynecologists advocate taking the endometrial biopsy at the very onset of menstruation to avoid interference with a chance pregnancy. However, this may be obviated by having the couple employ contraception during the studied cycle.

The *technic* of obtaining premenstrual endometrial tissue for histologic study is simple. One may employ, depending on his preference and technical ability, an endometrial biopsy forceps, or one of the specially-designed cannula-curettes—with or without suction, or the smallest fenestrated curette. Tissue should be obtained from at least three sites on the anterior and lateral walls of the uterine cavity to be certain of representative specimens, and should be fixed in Bouin's solution as soon as collected. The procedure should be preceded by a careful pelvic examination to exclude the presence of contraindicating conditions, such as cervicitis and adnexitis, and by sounding of the uterine canal to determine its length and direction. Aseptic technic should be employed. Moreover, once the curette has been introduced into the uterine cavity, it should not be withdrawn until the collection of the several specimens is completed. This precaution, lessening the opportunity to introduce infection, cannot be observed with the biopsy forceps. One of the curettes is, therefore, the preferred instrument.

The *interpretation* of the endometrial histology varies with the type of development observed. The endometrial patterns characterized by total absence of the secretory alterations indicative of ovulation and formation of a corpus luteum include all degrees of proliferation, hyperplasia and atrophy. The repeated finding of an atrophic endometrium premenstrually implies nonresponsiveness of the endometrium—a condition unrelated to anovulation. To differentiate anovular menstruation from the pseudomenstruation of nondeveloped endometrium, hormonal assays are required. The finding of normal urinary levels of estrogen and of pregnandiol, the excretion product of progestin, during the premenstrual period exempts the ovary and indicts the uterus.

When the diagnosis of anovulatory menstruation is established, either by temperature graphs or by repeated endometrial biopsies, or by both, its endocrine etiology should be sought in assays for pituitary gonadotrophin. If the ovary fails to ovulate because of a lack of pituitary gonadotrophin, none of the hormone will be found in repeated assays. On the other hand, if the ovary is primarily at fault and the pituitary gland is functioning normally, demonstrably increased quantities of gonadotrophin will be evident. Choice of therapy is thereby aided.

SUMMARY

1 A review of the current practices employed in the diagnostic management of the barren marriage is presented.

2 The necessity for the couple's initial orientation concerning the multiple etiologic factors of sterility, leading to the completion of a minimal diagnostic survey of each partner, is emphasized.

3 The method of conducting a systematic search for causative faults, including those of male infertility, of gross pelvic disease, of cervical insemination, of tubal occlusion, and of endocrine menstrual disorders, is stated.

4 The importance of a comprehensive history and the value of a thorough physical examination of each partner are affirmed.

5 The investigative tests employed in the diagnostic survey are described and evaluated. These include examination of the semen, testicular biopsy, study of the postcoital secretions, uterotubal insufflation, uterosalpingography, body temperature graphs, and biopsy of the endometrium.

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THE VALUE OF THE PERIODIC PELVIC EXAMINATION OF SUPPOSEDLY WELL WOMEN

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SINCE the days of Lady Montagu and William Jenner, medicine has been evolving from a profession devoted to the treatment of disease into a profession more and more concerned with the prevention of disease. The activities of the medical profession and of our public health service, improved methods of sanitation and improved living conditions have made diseases like smallpox, yellow fever, malaria and typhoid fever almost unknown in the practice of the average American physician. As a further result, there has been an amazing prolongation of human life from an average expectancy of thirty four years in 1800 to an average expectancy of sixty-four years in 1948.

It is evident today that the task of maintaining the health and usefulness of the large number of people whose lives have been so miraculously prolonged is an individual as well as a public health problem. The responsibility for maintaining the health and usefulness of this group rests very largely upon the individual citizen and his or her individual physician.

The prevention or early detection of the diseases of advancing years such as cardiorenal vascular disease and cancer is in reality a hand-to-hand combat, depending upon the frequent evaluation of the individual's physical fitness and the prompt recognition of deviations from the normal. To fulfill these requirements, the method of periodic physical examination of supposedly well individuals has been evolved. Nowhere in the body is this method more valuable than in the female pelvis.

EARLY DETECTION OF CANCER OF THE UTERUS

Sixty years ago cancer of the uterus was an incurable disease. Thanks to the development of radical surgery and the discovery of x-ray and radium, cancer of the uterus can now be cured. Whether a given woman is cured or not depends upon how soon her cancer is discovered and treated. Sixty to 70 per cent of cures in early cases dwindles down to no cures in late cases. More than 16,000 women died of cancer of the uterus in the United States of America last year. Many of these women might have been saved if their cancers had been detected earlier.

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Two methods are available for the early detection of cancer of the uterus. The first method consists in informing the lay public and reminding the medical profession that an irritating vaginal discharge, bleeding between periods or bleeding after the menopause may be symptoms of cancer and should lead to a pelvic examination.

As a result of the campaign of education carried on by the medical profession and by the American Cancer Society over the past thirty-five years, women with cancer of the uterus are coming earlier for examination. The number of hopeless cases—cauliflower growths or ulcerating craters occupying the vaginal vault—seen by the gynecologist has diminished.

The second method for the early detection of cancer of the uterus consists in the periodic pelvic examination of supposedly well women. Cancer of the uterus, as cancer of other organs, may run a symptomless course for an indefinite period of time. During this symptomless period the disease may progress beyond the reach of permanent cure.

VALUE OF PERIODIC PELVIC EXAMINATION—AN ANALYSIS

Ten years ago members of the Department of Gynecology of the Woman's Medical College of Pennsylvania, Dr Margaret C Sturgis, Dr Faith Fetterman and I, undertook a clinical research to determine the value of periodic pelvic examination in the detection of cancer of the uterus in the presymptomatic stage. A group of presumably well women enrolled as volunteers to help in the solution of this important medical problem. These were white women, 30 to 80 years of age, married or single, with or without children. All walks of life were represented but the majority belonged to the "white collar" group. The initial group numbered 1819.

Technic of Examination—The examination consisted in a careful bimanual vaginal examination and a careful inspection of the cervix in a good light. We painted the cervix with Lugol's solution (Schiller test) for the first 2000 examinations but then gave this up as it seemed possible to detect diseased areas without it. We did not use the Papanicolaou vaginal smear test because we wished to keep the examinations so simple that our conclusions would be applicable to the practice of every general practitioner in this country. At first we recommended a good many biopsies on inflammatory areas of the cervix. Later, as we became more convinced of the significance of these lesions, we recommended biopsy followed immediately by conization or excision of the entire erosion and subsequent careful microscopic study.

Results of Examinations—As was to be expected, some of the initial 1819 volunteers lost interest. Some moved away. Some died. Neverthe-

less, we are able to report on 732 women who have been examined more or less regularly over a period of ten years.

Displacements of Uterus or Vagina—While we were particularly interested in detecting cancer and lesions predisposing to cancer, we noted and recorded other abnormalities as well. The least serious of these were some 362 displacements of the uterus or vagina.

Benign Lesions of Pelvic Organs—Some 808 benign lesions of the pelvic organs were discovered from the beginning to the end of the research. These are listed in Table 2.

TABLE 1
DISPLACEMENTS OF UTERUS OR VAGINA

| | |
|---|-----|
| Retroversion of the uterus | 214 |
| Cystocele | 33 |
| Rectocele | 41 |
| Prolapse of the uterus | 28 |
| Cystocele and rectocele | 22 |
| Cystocele, rectocele and prolapse of uterus | 10 |
| <hr/> | |
| Total | 362 |

TABLE 2
BENIGN LESIONS OF THE PELVIC ORGANS

| | |
|---------------------------------------|-----|
| Inflammatory lesions of the cervix | 480 |
| Myomatous tumors of the uterus | 193 |
| Mucous polyps of the cervix | 130 |
| Cystic tumors of the ovary | 40 |
| Leukoplakic areas of the cervix | 3 |
| Papillomas of the cervix | 2 |
| Tuberculous ulcer of the vaginal wall | 1 |
| <hr/> | |
| Total | 808 |

A tuberculous ulcer of the vaginal wall was discovered on the seventh visit of a volunteer who had previously shown no pathologic condition. It appeared to be a slightly shotty, yellow area about three by four millimeters in diameter on the posterior vaginal wall, about one inch below the cervix. The patient was referred back to her attending physician who succeeded in demonstrating the tuberculous nature of the lesion. He reported that the volunteer's husband had been treated for tuberculosis of the kidney many years ago, had been symptom free and was considered cured. Husband, wife and attending physician are highly in favor of periodic pelvic examinations.

Most important of the benign lesions from the standpoint of cancer are the 480 inflammatory lesions of the cervix. These are classified in Table 3.

Some 214 of these inflammatory lesions have been eliminated by excision, conization or cauterization

Cancer—Only eight pelvic cancers developed in our 732 volunteers during the ten year period (Table 4)

In the first examination of the 1319 volunteers, four early cancers of the uterus were detected. Three of these were squamous cell carcinomas developing in areas of papillary erosion. One was an adenocarcinoma of the body of the uterus.

TABLE 3
INFLAMMATORY LESIONS OF THE CERVIX

| | |
|--------------------------------|-----|
| Endocervicitis | 68 |
| Cervicitis | 53 |
| Cervicitis with erosion—simple | 100 |
| follicular | 38 |
| papillary | 105 |
| not specified | 125 |
| Total | 480 |

TABLE 4
PELVIC CANCERS

| | |
|--------------|---|
| Cervix uteri | 4 |
| Corpus uteri | 2 |
| Ovary | 1 |
| Vaginal wall | 1 |

Four years later, a small area of adenocarcinoma was discovered on microscopic examination of a myomatous uterus removed from one of the volunteers.

On the eleventh examination of another volunteer, a smooth, red, polypoid growth was found projecting through the external os. The lady was symptom-free. The cervix had appeared normal at the time of her previous visit six months before.

A cancerous cyst of the ovary was discovered on the ninth visit of a volunteer and a cancer of the anterior vaginal wall was discovered by another volunteer (a physician) just before she was due for her fifteenth visit. No pathologic change had been detected at the preceding visit six months before.

The three cancers of the cervix first discovered were treated with radium, 3900 to 4500 mg hours, the patients are well, with no evidence of recurrence, after nine years. The fourth cancer of the cervix developed in a hypertensive individual who twenty-two years previously had been treated by radium for a bleeding myoma. After biopsy of her cervical growth, radium needles were inserted and subsequently an intrauterine

application of radium was made. She developed pyometra and general systemic infection after 3700 mg hours of radium. It became impossible to give her adequate treatment by either radium or γ ray. She left the hospital after a stormy course. She died after two years with recurrence in the abdomen.

The first patient with cancer of the uterine body was handicapped medically so that treatment was limited to radium and γ ray. She apparently remained well for seven years, had two strokes and developed recurrence of cancer after nine years.

The patient with microscopic evidence of cancer in a myomatous uterus removed by supravaginal hysterectomy shows no evidence of recurrence after six years.

The cancerous ovarian cyst was operated upon as soon as discovered but the cancer had already involved the adjacent peritoneum. The patient died from cancer after sixteen months.

The patient with cancer of the anterior vaginal wall was treated by excision and irradiation. She lived only three months and died of metastasis to the lung.

Comments.—As we review these cases, the fact that only four cancers of the uterine cervix developed in these 732 women is interesting. Some light is thrown upon this fact when we analyze the social state of the volunteers. We find that in the continuing group of 732, there were eighty single, nulliparous women, 113 married, nulliparous women and 539 parous women. Ten of the latter had been delivered by cesarean section whereby the cervix had sustained no trauma. This leaves a group of 529 parous women, 30 to 80 years of age, in whom one would expect to find more than four cancers of the cervix during a period of ten years.

The examining physicians attribute the low incidence of cancer of the cervix, in this group, to the discovery and elimination of 214 inflammatory lesions of the cervix. Our belief that cancer tends to develop in inflammatory areas has been strengthened by the fact that three out of the four cancers of the cervix discovered in our volunteer group were in areas of papillary erosion.

That these women could develop cancer is shown by the occurrence of ten cancers of the breast, six cancers of the intestine, one cancer of the parotid gland and two skin cancers.

On the basis of our ten years experience, the examining physicians are convinced of the value of periodic pelvic examination and are also convinced of the value of eliminating inflammatory lesions of the cervix. We recommend that every woman 30 years of age who has borne a child should be examined twice a year, that single women over 30 should be examined once a year, and that inflammatory lesions of the cervix should be eliminated.

AN EVALUATION OF THE CYTOLOGY TEST FOR UTERINE CANCER

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THE cytology smear method as an aid in the diagnosis of uterine carcinoma is being employed more and more in many clinics and hospitals throughout the country and is likewise spreading to various medical centers of the world. The accumulated experience of many competent workers indicates that this procedure has sufficient merit to justify a place as a laboratory test of considerable value, while at the same time the limitations of the method are also becoming better defined. In this respect it is important for the general practitioner, as well as the gynecologist and pathologist, to be thoroughly familiar with the merits as well as with the limitations of this test, for it is only natural that some over enthusiastic and dogmatic reports in the lay press have already done much to create too realistic a demand for it on the part of the public in the light of our present knowledge.

It is the purpose of this presentation to summarize an experience gained over a five year period during which more than 20,000 smears have been studied with particular reference to the many factors in technique and interpretation which tend to influence its accuracy, diagnostic value and usefulness.

METHOD FOR COLLECTION OF SMEARS

Smears may be collected from the posterior fornix of the vagina or the cervix. Vaginal smears have the advantage of representing material which has been shed from the entire genital tract, uterine tubes, endometrium, cervix and vagina with subsequent accumulation in the posterior fornix. It is essential that the patient shall not have douched for at least twenty four hours before such smears are collected. It is also im-

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portant that the pipette be introduced well into the posterior fornix if a representative sample is to be obtained Smears taken by personnel not experienced in this technic may contain only vaginal cells from the middle and anterior portion of the vagina Perhaps the chief disadvantage of the vaginal smear lies in the fact that a high proportion of the cells are of vaginal origin as compared with those arising from the cervix, endometrium or uterine tubes

Cervical smears may be collected in several ways by aspiration of material from the cervical os with a pipette, by using a cotton-tipped applicator, by scraping the surface of the cervical canal with a spatula such as that devised by Ayre² Cervical smears have the advantage of containing a high proportion of cells from the cervix proper and generally contain a goodly proportion of endometrial cells, particularly if the latter are being shed in increased amount On the other hand, they have the potential disadvantage of missing cells if a lesion should be present below the site of collection, furthermore, only material present in the cervix at the time the smear is taken may be present Smears collected by aspiration of the cervical mucus are somewhat more representative than those collected by the scraping technic, and are more likely to contain endometrial as well as cervical cells Conversely, cervical scrapings taken around the whole margin of the squamo-columnar junction of the cervix provide material in high concentration from the most common site of uterine carcinoma

It has been our experience that on occasion vaginal smears show abnormal cells not found on cervical smears while in other cases the opposite may occur For this reason we prefer to take three smears (1) from the posterior fornix, (2) from the cervical canal by aspiration, (3) cervical scrapings We believe from our experience that this combined technic affords the most reliable results

METHODS OF FIXATION

To obtain maximum results, smears must be fixed *before they have an opportunity to dry*, in a mixture of equal parts of ether and alcohol, and they should be permitted to remain in the solution for at least one hour However, smears may be kept in the solution for as long as two weeks without impairing the results If smears are to be sent to a distant laboratory through the mail, they may be fixed for one hour as described above, covered with a drop of glycerine and sealed with a second slide as recommended by Ayre,³ or after fixation the smear simply may be dried, mailed, and then stained with fairly satisfactory results without further treatment It is our opinion, nevertheless, that the best results are ob-

tained when the smears are kept in the fixing solution until ready for staining.

METHODS OF STAINING

Papanicolaou has done the pioneer work in studying a vast number of staining techniques for cytologic study of vaginal smears. It is generally agreed that the staining techniques which he has designated as EA 96^{*} and EA 50^{*} are the most satisfactory. In our experience EA 86 permits better interpretation of the estrogen effect because of more clear-cut differentiation between eosinophilic and basophilic cells. EA 50, which is commercially available,* in some instances appears to give a better transparency, possibly because of the special solvent employed.

CRITERIA OF MALIGNANCY ON CYTOLOGIC SMEARS

Unfortunately, there are no *absolute* criteria for making a positive diagnosis of malignancy on the basis of cytologic smears; indeed, the interpretation must be made on an evaluation of numerous findings. Unquestionably the personal factor in cytologic interpretation is of far greater import than that which obtains in making a histologic diagnosis of malignancy. Space does not permit of a detailed discussion of the various factors that influence cytologic interpretation, but the more important of these may be summarized as follows:

1 Abnormalities of the Nucleus.—It is generally agreed that changes in the nucleus are most important so far as the interpretation of malignancy is concerned. These include absolute increase in the size of the nucleus, marked variation in nuclear size, nuclear deformities, fragmentation of the nucleus, hyperchromasia, disproportionate increase in size and prominence of the nucleolus, prominence of chromatin and a tendency for the latter to be distributed around the edge of the nucleus, an increase in mitotic figures (though this is of far less significance than in histologic diagnosis), and an increase in multinuclear forms.

2 Changes in the Cytoplasm.—These include marked variation in the size of the cell, a tendency for cells to be abnormally large, irregularities in cell margin and marked variation in the shape of cells revealing many unique or bizarre forms. Peculiarities in staining reaction, increased vacuolization of cytoplasm, and evidence of necrosis and degeneration likewise occur in some of the cells.

3 Associated Findings.—In addition to the cytologic changes suggesting malignancy there are other factors frequently found in smears of

* May be obtained from Ortho Products, Raritan, N. J.

patients with carcinoma, but not in themselves of primary diagnostic significance since they can be found in other conditions but which occur as follows red cells and blood pigment, an increase in leukocytes, an increase in histiocytes and macrophages, a tendency for abnormal cells to be present in clusters with "crowding" of cells, and the presence of large giant cells or a syncytium of cells

In addition to the many factors listed above which require evaluation, the difficulties of recognizing the many types of normal cells which one may find in these smears, as well as recognizing their site of origin, must be emphasized. To learn the wide range of normal requires considerable time and experience, and this is essential before one can undertake to interpret the changes induced by malignancy. In addition, the many bizarre cells which may occur as the result of infection in various parts of the genital tract, or in association with various benign growths, as well as changes resulting from hormonal therapy or after irradiation with α -ray or radium, make the task of interpretation still more difficult. It is for this reason that in our experience the training of pathologists in the cytologic diagnosis of uterine carcinoma requires at least six months of diligent study of smears even after an initial "indoctrination" course of several weeks. Even in experienced hands the reading of cytologic smears is a time-consuming task requiring as much as twenty to thirty minutes if abnormal cells are present, and at least five to ten minutes to thoroughly check negative cases. A well-trained and vitally interested technician may be of invaluable service in making a preliminary study of the slide and marking abnormal fields for study by the pathologist.

4 Reporting of Results—Because of the difficulties of interpretation enumerated above, most workers in this field are reluctant to report smears on the basis of "positive" or "negative" alone, and as a consequence various systems of grading have been suggested to indicate the relative probability of malignancy. Some employ the terms "positive," "doubtful" and "negative"; we have been routinely employing four types of grading, namely "positive," "suspicious," "doubtful," and "negative." Papanicolaou has suggested a system of grading of one to five. It is apparent, therefore, that the interpretation of the result by the clinician depends upon his familiarity with the criteria employed by the cytologist and as a consequence close liaison and discussion of questionable smears is often necessary.

EVALUATION OF REPORTED STATISTICS

A considerable number of reports have now appeared on the evaluation of the accuracy of the cytologic technic in the diagnosis of uterine carcinoma. We have recently pointed out¹⁰ that figures on the "over-all"

accuracy of the technic have comparatively little significance, unless viewed in conjunction with the percentage of correct 'positives,' the percentage of correct 'negatives,' the type of patients being studied, and the comparison with the *histologic* diagnosis. For instance, in some "screening" studies where the number of patients is large and the number of malignancies small, excellent over-all results can be expected since, as a rule, false positives are much less common than false negatives. On the other hand, in studying patients routinely admitted to a gynecologic service in whom the incidence of pathologic lesions both benign and malignant is high, and in whom unusual or abnormal cells may appear on almost every slide, the percentage of false positive smears may be quite high, particularly when read by cytologists of recent or limited experience. The opposite difficulty, namely, missing many positive cases, has been one of the disturbing factors noted by some workers as their experience has increased, since the tendency is to become more and more

TABLE I

RESULTS ON 500 CONSECUTIVE WARD PATIENTS READ AS "UNKNOWN" USING A SINGLE SET OF VAGINAL SMEARS

| | |
|------------------------------|--------------|
| Total number of patients | 500 |
| Patients with uterine cancer | 63 |
| Correct results | 474 or 94.8% |
| Correct positives | 44 or 70.0% |
| Correct negatives | 430 or 89.4% |
| False positives | 7 or 1.6% |
| False negatives | 10 or 30.0% |

cautious in making a diagnosis of "positive" as one becomes more and more aware of the large normal variation and the unusual or bizarre forms which can be found in many benign conditions.

At the recent Boston conference on the cytologic methods of diagnosis of cancer sponsored by the American Cancer Society,¹ marked variations were very evident in the statistics presented. In a report compiled from fifteen different sources representing a total of 22,700 cases, the average percentage for false negatives was 11.6 with a variation ranging from 0 to 30 per cent, false positives averaged 1.1 per cent with a variation of 0.7 to 2.3, although the writers are aware of other unpublished studies in which false positives ranged as high as 6 per cent. Many factors contribute to these wide variations, even when the slides are read by the same individuals. For instance, in our own institution in a report of 500 cases in which only a single set of smears were taken on all patients as they were admitted to the gynecologic ward, and without knowledge of the age of the patient, her admitting diagnosis date of the last men-

strual period or previous hormonal therapy, the results were as shown in Table 1

On the other hand, in a more recent study from the same ward in which all of the above data were available and with repeat smears made on all doubtful and suspicious cases, false negatives have averaged approximately 10 per cent and false positives have averaged approximately 15 per cent. This comparative study indicates that a single, one smear technic without knowledge of all clinical factors involved should never be adopted as a routine laboratory test, and thus be relied upon as a basis for treatment.

TABLE 2

RESULTS OF CYTOLOGIC SMEARS AS A "SCREENING" TEST IN CANCER DETECTION CLINICS (July 1944-March 1948)

(These results cannot be considered final since "follow up" is not yet complete)

| | |
|---|--------------|
| Number of patients | 4,947 |
| Number of smears | 12,320 |
| Number of patients with uterine carcinoma | 7 |
| Correct positive smears | 6 or 85 7% |
| Correct negative smears | approx 99 5% |
| False positive smears | 2 |
| False "suspicious" smears | 18 |
| "Doubtful" smears | 13 |

Finally, in a screening study done in our laboratory utilizing material obtained from various cancer detection clinics under the auspices of the Donner Foundation, the results given in Table 2 were obtained.

RELATIVE VALUE IN VARIOUS TYPES OF PELVIC MALIGNANCY

It is well established that the cytology smear method is more accurate in the diagnosis of cervical carcinoma than in endometrial cancer. Thus Fremont-Smith and his co-workers report that of 285 cases of cervical cancer, thirty-one (10.9 per cent) were missed by smear while in ninety-eight cases of endometrial carcinoma the smear was negative in twenty cases (20.4 per cent). In our own laboratory, "missed" fundal cases have ranged from 15 to 33 per cent in different groups of patients, averaging about twice as high as missed cervical cases. There are several factors which contribute to this disparity. In the first place cervical cells accumulate in greater numbers in the posterior fornix of the vaginal than do endometrial cells and can be more readily obtained by direct scraping of any suspicious areas. Perhaps more important is the fact that the criteria for making a diagnosis of endometrial malignancy are far more subtle than in cervical carcinoma. In endometrial cancer the abnormal

cells do not as a rule show the same degree of bizarreness in size and shape of cells and are likely to have gross nuclear abnormalities. The diagnosis of endometrial malignancy is largely dependent upon detecting an increase in the size of cell and nucleolus, intensity of staining reaction and relatively subtle changes in nuclear form.

Sarcoma of the uterus may give rise to distinctly unusual and bizarre types of cells which arouse the suspicion of malignancy even though its exact form may not be recognized. In tubal malignancies, also, bizarre cells suggestive of cancer have been reported by a number of observers and have led to exploratory operations which have demonstrated the tubal lesion. Cytology smears are ordinarily of no specific value in ovarian malignancies, although in estrogen producing tumors a strong estrogen effect may be obtained.

SMEAR VS BIOPSY

On the basis of the experience represented above, it is our opinion that at the present time the vaginal smear report should not be used as a final diagnostic criterion. It is quite apparent that, even in the hands of those who have used the method most, cytologic diagnosis does not have a total accuracy comparable to that obtained by standard histologic methods. In our opinion the real value of the vaginal smear lies in uncovering more patients who should have biopsy and/or diagnostic curettage, in order to ferret out lesions that otherwise would have been missed. We are of the firm conviction that any patient who presents symptoms or clinical findings suspicious of malignancy must be thoroughly investigated by these well established standard techniques regardless of the smear report. We regard a positive smear as evidence that the patient must be further investigated. Just as a suspicious lesion cannot be ignored, so must a repeatedly positive vaginal smear be adequately explained. There are now sufficient cases on record, and we ourselves have had a number of such, in which a positive smear was the only indication of malignancy. In one such case, initial biopsy proved negative. A subsequent and more adequate biopsy was taken because positive smears persisted, and finally showed a clear-cut picture of carcinoma of the cervix. On the other hand, negative smears in the presence of advanced carcinoma have occurred on repeated occasions and indicate plainly that a negative smear does not rule out uterine malignancy.

CARCINOMA IN SITU

The opinion has been expressed that cytology smears may prove to be particularly valuable in the diagnosis of very early lesions of the cervix,

especially carcinoma-in-situ. Thus Hertig⁶ found eight positive smears in thirteen cases of pre-invasive carcinoma of the cervix. Fremont-Smith, Graham and Meigs⁴ report positive vaginal smears in fifteen of seventeen cases of pre-invasive carcinoma of the cervix and state that of thirteen biopsies taken from these seventeen patients, the histologic diagnosis on the initial biopsy was positive in only five. Four of the patients had no symptoms, a neoplastic lesion was unsuspected and discovered only by routine vaginal smear. On the basis of their findings, these authors venture the opinion that, in the diagnosis of very early carcinoma of the cervix, the vaginal smear is not infrequently more accurate than the biopsy.

Statistics such as those reported above can prove very misleading unless interpreted with considerable caution. Since false positive smears are not at all rare, unnecessary operations and irradiation therapy may be undertaken if smears are interpreted at their face value, and treatment instituted forthwith. Indeed, the authors are aware of several such operations in which hysterectomy was largely, if not entirely, influenced by a single positive smear. We are at present of the opinion that even when the cytology smear is persistently positive, repeated biopsy and curettage are the procedures of choice rather than the immediate institution of treatment for cancer on the basis of smear diagnosis alone.

THE USEFULNESS OF THE CYTOLOGIC SMEAR IN NONMALIGNANT LESIONS

In addition to its place as a diagnostic aid in carcinoma, the vaginal smear is of considerable value as a routine procedure in all gynecologic patients for the general information it affords. In this respect it occupies a place comparable to the routine urinalysis and blood count. One is able to determine such things as the relative degree of ovarian function or the presence of an inflammatory reaction in the genital tract. Often trichomonads or monilia can be demonstrated on the smears. Increased numbers of cells from the cervix or endometrium and the presence of blood cells or blood pigment may attract attention to a benign as well as to a malignant lesion.

PLACE OF THE CYTOLOGY SMEAR AS A SCREENING PROCEDURE

One of the most important purposes served by the cytologic smear method is the detection of suspicious cells in patients who have no symptoms or observable lesions. In this respect it would seem that the cytologic method deserves an important place in the screening of large numbers of patients for uterine malignancy. Several large scale studies are under way in cancer detection clinics in which the cytologic smear is used

as a routine test in addition to the usual and accepted methods of examination. Thus far, there is some question as to whether the technic will prove worthwhile from the standpoint of effort expended and expense involved in relationship to the number of unsuspected cases detected. In the examination of almost 5000 patients (Table 2) we have to date detected six positive smears, however, in only one of these patients was the lesion entirely unsuspected. In the other five patients, symptoms or lesions sufficiently suspicious to warrant curettage or biopsy were present. In a study being conducted by the Massachusetts Health Department, it is estimated by Lombard⁷ that a probable one to two symptomless cases in 500 women will be found.

On the basis of these statistics it has been questioned as to whether the cytology test will prove practicable as a screening method. In this respect it is only fair to point out that the value of the method should not be considered merely in terms of positive cancer cases detected but in the light of benign lesions that may be found as well, and which need correction. Negative smears are also of some significance and in fact, from a statistical standpoint, the results with negative smears are more accurate than in the 'positive' cases. Furthermore, as pointed out above, the smear is of general value in other respects. Also repeat smears taken at six month intervals, as is the practice in our cancer detection clinics in Philadelphia, may yield information of considerable value with regard to the detection of early lesions when serial smears are compared.

VALUE OF SMEARS FOR FOLLOW UP

Cytology smears may have a very real place in evaluating the progress of the patient after treatment with radium or x ray. In favorable cases the vaginal smears become negative within a matter of weeks after treatment has been given, while in patients who fail to show a favorable response, positive smears may persist indefinitely. Some difficulties are encountered in the interpretation of smears after irradiation because of changes in the cells which are believed to be due to 'irradiation effects'. The chief effects appear to be an increase in the number of necrotic and degenerated cells, peculiar staining reactions of the cytoplasm, and an increased number of phagocytic cells. Very often these irradiation effects are quite marked and persist for many months after treatment and may influence the interpretation of smears. Some workers⁸ have attempted to correlate the radiosensitivity of the malignant lesions on the basis of the cytologic characteristics of the abnormal cells prior to therapy. It is as yet too soon to say whether such attempts at correlation will prove useful, for radiosensitivity is not synonymous with radiocurability.

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OBSERVATIONS ON THE DELAY PERIOD IN THE DIAGNOSIS OF PELVIC CANCER

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INTRODUCTION

The ancient Greeks realized that cancer could be extirpated only in its initial stage. Since these early times this same observation has been made frequently and elaborated upon. Current writings on cancer seldom fail to reiterate the importance of early diagnosis and its relation to cure. In discussing the factor of delayed diagnosis in pelvic cancer, Novak¹ states that "it seems almost banal to elaborate on it." He further states that he prefers to spend little time discussing this subject "because it is so self-evident and because it has been urged so long, so widely, and so forcefully."

In spite of the wide knowledge of the delay period in the diagnosis of cancer, little, if any, change has been noted over the years. The mortality statistics on cancer of the uterus, for example, show no improvement in the last decade. The situation remains static even though there have been widespread educational programs designed to decrease this costly time interval.

Pleck and Grillo² pointed out in 1938 that the physician and the patient shared the responsibility of the delay period. Burke,³ Pratt,⁴ Lynch and Robbins,⁵ have more recently discussed the relation of the physician to this subject. The astonishing fact remains that, in spite of this very plain and obvious situation in the cancer problem, so very little has been accomplished.

The lay educational program seems to be making some headway. Lynch and Robbins⁶ concluded from a recent survey that the education of the public is showing results whereas the physician is not responding. This is concluded from the comparison of a survey made in 1944 with a similar study conducted in 1938. More frequent requests by patients for periodic examinations and the popularity of the cancer detection clinics are concrete examples of the influence of cancer education on the public.

The problem of the physician is another subject. That the physician does contribute to the delay in diagnosis of pelvic cancer cannot be

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denied. Miller⁶ writes on this subject quite frankly. He points out that most physicians are not aware of their responsibility in the general cancer problem. Physicians, by doing periodic pelvic examinations on all patients after the age of 40, "have within their grasp the means to exert a powerful influence on cancer of the female genitalia." Early detection and prevention is the answer to cancer control and it is up to the physician to play his role in this fight in a degree commensurate with his responsibility. Novak¹ feels that the physician has a "curious lack of responsibility for the patient's welfare, a mental apathy or lack of conscientiousness which leads the physician to drift along rather than to buckle down intensively to the solution of this problem."

The solution to this problem lies in a practical educational program based on a study of the problems confronting the general practitioner in the early diagnosis of cancer. An attempt has been made in Philadelphia to undertake a program designed to accomplish these objectives. The Committee for the Study of Pelvic Cancer⁷ is working in Philadelphia to study and to reduce, if possible, the delay period occurring in pelvic cancer cases. The true facts concerning the delay period are obtained for this Committee by direct contact with living cases of pelvic cancer and by direct questioning of the physicians consulted by these patients. The uniqueness of this program has to do with dealing with the practicing physician. Heretofore information of the delay period has been obtained from hospital records or from the patient. The frequent biased and inaccurate patient reports led to improper appreciation of the true facts. The primary purpose of such an approach is to analyze the reasons for physician delay, not to be critical of his handling of the patient, but through an appreciation of the problems attempt to offer constructive suggestions whereby the same delay might be avoided in the future. By this approach we are not only finding the cause of delay but at the same time instituting a practical educational program for the physician. It is educational in that the general practitioner is sensitized to the important role he plays in the cancer field, he is made more "cancer conscious," and open discussion with the Committee makes for a better understanding of the problems involved in early cancer diagnosis.

RESULT OF EDUCATIONAL PROGRAM

During the past two and one-half years 1000 patients with pelvic cancer have been questioned in regards to the diagnostic delay period. Both the patient and the physician delay have been analyzed. This paper will refer specifically to the problems confronting the physician. This discussion will deal with the time interval elapsing between the first visit of the

patient to the physician until an adequate diagnosis is made. A lapse of time of more than one month is considered excessive and labeled as undue delay on the part of the physician.

Analysis of Physician and Patient Delay—Table 1 shows briefly an analysis of the 1000 cases. It should be noted that these cases are taken from the Out-Patient Departments and Wards of twenty-one different hospitals in all sections of Philadelphia and can be said to be representative of the general pelvic cancer population in this city. It will be noted that physician delay occurred in 276 instances. This figure establishes the importance of the problem under discussion and the pressing need for persistent corrective measures. More impressive is the realization that better than 4000 patients a year with cancer of the uterus in the United States may be victims of delayed diagnosis on the basis of these figures. The average delay period for this series of cases was 14.9 months.

TABLE 1
ANALYSIS OF PHYSICIAN AND PATIENT DELAY IN 1000 CASES

| | No. of Cases | Percentage |
|-----------------------------|--------------|------------|
| Physician delay | 158 | 15.8 |
| Physician and patient delay | 118 | 11.8 |
| Patient delay | 437 | 43.7 |
| No delay | 287 | 28.7 |

TABLE 2
AVERAGE DELAY FOR VARIOUS SITES OF PELVIC CANCER

| | |
|--------|-------------|
| Vulva | 27.0 months |
| Fundus | 13.7 months |
| Ovary | 11.2 months |
| Cervix | 7.8 months |

Average Delay for Various Sites of Pelvic Cancer—Table 2 indicates the average delay found for the several sites of pelvic cancer. Curiously enough, the patients with the most accessible lesion experienced the longest delay. The injudicious use of salves and local treatments of the vulva account for this figure.

Factors in Physician Delay—*Incorrect Diagnosis*—The factors leading to delay by the physician are many and varied. Some of them are excusable. A physician may make the wrong diagnosis, which in turn leads to the wrong treatment, to the wrong advice or to no advice and many other errors. No one is infallible and to pass judgment or to criticize on the basis of these factors seems unreasonable. No doubt as long as physicians are human mistakes will be made. If the correct diagnosis is made, however, and inadequate treatment is given, this is

certainly an improper discharge of the physician's responsibility to his patient. The greatest benefit will come, therefore, from the education of physicians in the latest methods of diagnosis and to the established and accepted methods of treatment. Failure to employ the available diagnostic aids when indicated and to apply proper therapy in known cancer cases constitutes an undeniable lack of conscientiousness.

Failure to Examine in Presence of Pelvic Symptoms—The greatest single factor for which the physician can be justly criticized is his failure to do a pelvic examination in the presence of pelvic symptoms. Of the 276 patients in which physician delay occurred, 51.7 per cent or 142 cases were not examined internally. The failure to make a pelvic examination in the presence of pelvic complaints cannot be passed off lightly and from the physician's standpoint cannot be logically explained. A more serious aspect is added to this phase of the delay problem when it is pointed out that 45.8 per cent of these patients (65 cases) were postmenopausal and their chief complaint was a recurrence of bleeding following a previous cessation of the menstrual period. This latter infraction of the principles of good medical practice emphasizes the seriousness of the problem at hand.

The explanations for failure to perform a pelvic examination, when indicated, should be examined closely and made the basis for any educational program offered to the medical profession. Concerted action to remedy these known errors will result in earlier diagnosis and hence an increased salvage of these cancer patients.

Reasons Listed for Failure to Examine Patients—The outstanding reasons given by physicians in explanation for their failure to examine patients in the presence of pelvic symptoms are analyzed below.

Presence of Active Vaginal Bleeding—The presence of active vaginal bleeding is considered by many as a reasonable excuse to defer pelvic examination. There is no medical reason for not examining a patient, under these circumstances. An examination at this time would more readily divulge the source of the bleeding. Postponement of the examination may result in delay in making an early diagnosis. These patients are usually given some form of medication at this first visit. A remission of bleeding is interpreted by the patient as indicating an inconsequential cause for her complaint and hence may mean she will not seek further advice until symptoms recur. Then it may be too late. The loss of irrevocable time in diagnosing cancer demands that every opportunity afforded a physician for making a diagnosis must be accepted. Further lay education will teach patients to present themselves and to expect an examination in the presence of bleeding. Physicians must practice it now.

Indiscriminate Use of Medication—So many cases presented for discussion indicate that pelvic symptoms are treated without any attempt at a diagnosis. Vaginal discharges, for example, are treated at times by douches with a warning to the patient to return for a pelvic examination if symptoms do not abate. Physicians complain that patients have failed to follow their advice, but feel satisfied that they have discharged their duty adequately with this warning. Could not the patient justly complain that a pelvic examination had not been made at the first visit? More logically she could argue that if a pelvic examination was indicated in the presence of persistent symptoms it certainly was indicated at the time the symptoms were first reported. Medication in any form for the symptomatic relief of pelvic complaints is to be condemned until every effort to establish a diagnosis has been made. The most fundamental approach to the diagnosis of pelvic disease is an adequate pelvic examination at the earliest possible time.

The physician is personally responsible in many instances for the failure of his patients to comply with his request to return for examination. Patients interpret the actions and advice of the physician in terms of what they want to believe. A casual approach to the patient's problem is interpreted as an indication that her complaints are not serious and further concern is not warranted. If an early carcinoma is present at this time, certainly a delayed diagnosis weeks or months later may mean the difference between life and death for that patient.

Failure to Examine at First Office Visit—Failure to examine the patient at her *first* visit regardless of other considerations already discussed is in itself a major cause of delayed diagnosis of pelvic cancer. Fear often causes patients to delay in seeking advice. When sufficient courage and determination are mustered and the patient presents herself reluctantly, the opportunity for an adequate examination must be taken. It has been found that failure to take this original opportunity may be very costly to the patient. If she is treated casually by the physician, she will surmise her concern has been exaggerated and interpret no examination as indicating her complaints are not of a serious nature. In some instances no examination is suggested whereas in others the patient is told to return at another time for this procedure. In either case long delays are the result because these patients either never were offered an examination or they fail to return as suggested. In the fight against cancer the physician must make the most of every opportunity when it *first* presents itself.

Patient Unprepared for Pelvic Examination—Some patients make this claim at the first visit. The physician may be forced in these circumstances to postpone the examination until a later date. Unless a

definite appointment for this examination is made the patient may not return. It is the physician's duty to follow-up the patient if she fails to appear for her appointment. An important point to emphasize is that no medication should be given to the patient who refuses a pelvic examination at her first visit. It has been shown in this series of cases as well as elsewhere that patients who are not examined and who are refused treatment are more likely to return at the appointed time than those who are given treatment, and if they do not return to the first physician are much more likely to seek help elsewhere.

Symptoms Indicative of Menopause—The reassurance to the patient that her complaints are due to "the change" is a very serious and oft-repeated cause of physician delay. The willingness to ascribe most any symptom or group of symptoms in the 40–55 age group to the effect of the menopause is a common practice. It is mentioned only to be condemned. The common practice of prescribing hormone therapy without a previous adequate pelvic examination is one of the great blots on the record of the present day physician. The fault is so obvious and so prevalent that one ponders seriously the motives behind present day medical practice. The high incidence of pelvic cancer during and following the menopause demands that special efforts be exerted by all physicians to discharge conscientiously their duty to these patients.

Patient Visited at Home—Patients with pelvic symptoms are at times first seen in the home. It is the common practice for a pelvic examination to be deferred on this basis. The physician treats the patient and wisely advises her to come to the office for a pelvic examination. In many instances the patient fails to appear for an examination. After spending some time in bed and taking the prescribed medicine the patient feels better, symptoms abate and no examination is requested. A pelvic examination can be and should be done in the home. It may not be quite as convenient or as satisfactory as in the office but the physician who does examine his patient under these circumstances is at least trying to discharge his duty in a conscientious manner. It appears, therefore, that a pelvic examination may be deferred on the slightest provocation. It is one of the strongest weapons we can wield in the fight against cancer and in early diagnosis, yet we fail so often to make use of it.

Delay in Examined Case—The importance of examining patients has been discussed. An examination does not unfortunately insure against a delayed diagnosis of pelvic cancer. A diagnostic delay in an examined case may result for several reasons.

Incomplete Examination—An adequate pelvic examination means bimanual vaginal and abdominal palpation, adequate visualization and inspection of the vagina, the cervix and the external genitalia. Delay may result from a failure to carry out routinely the complete examination.

Unfortunately, even a complete pelvic examination does not always prevent a delayed diagnosis. Patients with pelvic complaints in the face of no gross pathologic changes have been advised to await further developments. This proves particularly hazardous in the postmenopausal patient who complains of intermittent vaginal bleeding with no evidence of the bleeding at the time of the examination. Patients in this category should be subjected to more complete investigation than that offered by a single office examination.

Incorrect Diagnosis—A pelvic examination may, on the other hand, disclose gross pelvic disease which may be incorrectly interpreted. Delay in cancer diagnosis will result when an early cervical cancer is thought to be a benign cervicitis and treated as such. The indiscriminate and wide use of hormones contributes frequently to errors in diagnosis. The occurrence of bleeding in patients subjected to hormone therapy may be interpreted to be due to the medication. Such patients are candidates for serious delay. These cases cannot be treated casually but every effort must be made to rule out malignancy. A high index of suspicion for cancer will be the only insurance against such catastrophes. Such errors in diagnosis might seem to fall into the excusable realm. If pelvic cancer is to be diagnosed early and treated adequately, these common errors of omission must be eliminated.

Wrong Treatment Following Correct Diagnosis—A serious delay may occur in some instances in the presence of a correct diagnosis. Failure to institute adequate therapy has contributed to results comparable to those from delayed diagnosis. Inadequate surgery or irradiation in the presence of a known cancer is inexcusable. Failure to refer the patient for adequate therapy when equipment at hand is inadequate has caused needless delay. The pessimistic outlook by some physicians has led them to withhold therapy, expressing this by saying, "What's the use?" This attitude is mentioned only to be condemned. Of what avail is an early diagnosis if the cancer is to be inadequately treated?

It is the habit of some physicians, when referring cancer patients to a clinic or specialist for therapy, to instruct the patient to make this contact with the consultant. To insure a prompt course of action, the referring physician should contact the specialist and see that early and prompt contact with the patient is accomplished. The responsibility must not be left to the patient. In cases where this has been done, long delays before institution of treatment have occurred.

CONCLUSIONS

As noted from the foregoing discussion, the importance of an early diagnosis with the least possible delay cannot be overemphasized. The following conclusions are made:

The physician must become more "cancer conscious." The general practitioner is through necessity the one to see the majority of cancer patients first. His actions and advice may determine the ultimate life and death of the patient. Physicians in this vital position must be adequately prepared to diagnose and properly advise or treat the early cancer patient. It must be recalled that the earlier the cancer lesion is seen, the more difficult is the diagnosis. This demands a definite cancer awareness and a knowledge of current methods of diagnosis and treatment. To accomplish the discharge of his duty properly, the physician is urged to know and practice the following rules to help avoid unnecessary delay in diagnosis.

- (a) Examine all patients with pelvic complaints. Periodic examination of women over 40 regardless of complaints should be urged.
- (b) The treatment of pelvic complaints must be withheld until an adequate diagnosis is made.
- (c) A pelvic examination must be made, if at all possible, at the time of the first visit.
- (d) The examination must be complete—the use of bimanual palpation, a speculum and a good light.
- (e) Patients actively bleeding should be examined in the presence of this complaint. No contraindication exists for this practice.
- (f) If a patient refuses examination, she should not be treated. The patient may seek help elsewhere if so managed and ultimately submit to examination.
- (g) A suspicious cancer lesion should be studied relentlessly until a definite conclusion is reached.
- (h) In the presence of known cancer, proper therapy must be promptly instituted.
- (j) Arrangement for clinic or specialist care of cancer patients must be made by the referring physician. The responsibility must not be placed on the patient.

SUMMARY

- 1 Culpability for delay in diagnosis of cancer is shared by the physician.
- 2 Education of the physician in his responsibility to the cancer problem is necessary.
- 3 A practical educational program for the physician is discussed briefly.
- 4 Factors leading to delayed cancer diagnosis are reviewed.
- 5 Remedial measures to decrease the diagnostic delay in pelvic cancer are suggested.

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PSYCHOSOMATIC APPROACH TO GYNECOLOGIC PROBLEMS

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THE title would suggest that gynecologic problems can be approached with emphasis on the psychosomatic aspects as opposed to a more purely organic orientation. As a matter of fact, the modern medical man no longer attempts to maintain a dichotomy between mind and body but, by necessity, must view the patient as an integrated individual in whom emotional factors influence physiological responses, or organic pathology impinges upon psychic function. Only by having a thorough knowledge of the patient's physical and mental make-up can the symptoms be evaluated adequately.

That psychic factors play a prominent role in dysfunction of the physiology of the pelvic organs is understandable when we consider the many restraints our culture imposes upon the free expression of the individual's natural development. For example, because of lack of preparation and guilt feelings centered around sexual matters, many girls fear and resent the onset of menstruation and some unmarried women rebel against each menstrual period as a recurring reminder of the frustration in carrying out their full physiological role. This was well exemplified by a thirty three year old school teacher who was incapacitated several days each month by severe menstrual colic and low back pain. It was suggested that if she really wanted a period, pain might be absent—a thought which was vehemently rejected. Some months later, after an indiscretion, her obvious desire for menstruation culminated in a painless period.

The influence of wishes and strivings, the strength of which are not recognized consciously by the patient, play a large role in influencing daily activities and the development of a complaint problem. A simple example of this principle is the frequency with which dental and psychiatric appointments are broken or neglected as compared to social engagements. These motivations which govern behavior in everyday life operate in a more subtle way in symptom formation. For these reasons we often cannot accept at face value an individual's evaluation of his symptoms and statements negating psychic factors. Patients oftentimes vehemently

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protest the absence of emotional conflict while actually the symptom may represent an ineffectual attempt to solve that conflict

MENARCHE

Biologically and psychologically the girl begins to function as a woman at puberty. Now the growing child who formerly may have rejected the feminine role has objective proof of her sex. Confronted by a reality which she can no longer deny consciously, she may rebel psychologically against the painful female role by suffering pain with each succeeding period. She may even go so far as to retard the onset of puberty. Reider¹ reports a case of delayed menarche in a 15 year old girl brought to the Neuropsychiatric Division of the Topeka Municipal Clinic for treatment of a long-standing depression. After one psychotherapeutic interview, when her guilt feelings and tension were relieved, menses began.

From time immemorial the menstrual period has been surrounded by strange taboo and superstition (Chadwick²). In some cultures women during their menses were forced to withdraw from the household and were believed to wither flowers, sour milk and putrify meat. Even today in certain segments of our society it is not rare to encounter someone who feels that he will lose his manhood if he has intercourse with a menstruating woman. In spite of the fact that we are considerably more enlightened, the preparation for the menarche too often is hardly more logical than the old folklore.

Although it is obvious that every girl should have the opportunity to acquire the biological facts pertaining to menstruation, it has to be borne in mind that the adequate utilization of this information is not possible unless she has also been prepared emotionally to make use of it. It is not enough for the parent, the teacher or the physician to propound these facts, they must be presented by someone with whom the child has a healthy emotional relationship. We recall the preadolescent girl in a professional family to whom the parents suggested she read deSchweinitz's "Growing Up."³ This she refused to do, stating that she wanted her mother to explain the matter.

Frequently the girl's first period is accompanied by feelings of shame, guilt, remorse or fear of having been injured. This is particularly true in girls who have been punished by their parents for some simple normal expression of sexual curiosity. The harsh, stupid fashion with which childhood masturbation is handled by some parents not infrequently causes guilt feelings which persist and subsequently interfere with the expression of sexuality in its mature form.

AMENORRHEA

That the menstrual cycle, once established, is often interrupted or altered by emotional forces is well known. The nature of the relationship between these forces and the associated endocrinological changes is still a moot question. As an example of this we observed an attractive 16 year old girl whose foreign born parents attempted to enforce rigid old world mores in a new world culture. The resulting conflict culminated in a quarrel between mother and daughter when the former learned that the girl had been dating surreptitiously. Guilt feelings, already present, were heightened by the mother's recriminations during an argument and reached a climax when the mother fainted. The girl thought she had died and responded by becoming highly hysterical. Thereafter she did not menstruate for a year and, further regressing to an infantile level of behavior, satisfied her aggressions by developing an excessive appetite with resulting obesity. Thus she became unattractive to men and thereby avoided the further temptation to rebel against the old mores. Her oral cravings can well be interpreted as a displacement of her sexuality. The patient was studied in the Endocrine Clinic at Jefferson Hospital, Philadelphia, where no physical cause for the obesity or amenorrhea could be found. Hormonal assays revealed definite evidence of depression of pituitary function which the endocrinologist suspected to be of psychic origin and referred the patient for psychiatric study before attempting hormone therapy. Since the relationship between the psychic forces and the complaint problem seemed in this case so obvious, psychotherapy appeared to be indicated—at least as a preliminary form of treatment prior to endocrine therapy. The results were startling, since almost immediately after the patient began to feel relieved of guilt and was able to accept her sexuality, the menses were reestablished, appetite diminished, weight loss began and normal social relationships were resumed. Several interviews with the mother helped her to develop considerable understanding of the patient's normal needs and gained her cooperation. Within three months recovery was complete, the girl having achieved a fully satisfactory adjustment in her environment. The hormonal assays were then normal.

DYSMENORRHEA

An evaluation of the symptom dysmenorrhea must embody a consideration of the woman's entire attitude toward womanhood (Deutsch¹). Menstruation is the badge of femininity and the badge may be worn in disappointment, pain or pride depending on the attitude of the woman.

The significance of menstruation to women can be viewed from the standpoint of their orientation toward childbearing. The girl who looks upon menstruation as a milestone in the process of growing up and eventually having children is not so likely to be troubled by painful periods. In the woman who desires a child but for some reason or other has none, the period may produce feelings of depression. Menstruation has been called "the weeping of the disappointed uterus" (Gill⁶) On the other hand, the woman who rejects childbearing frequently exhibits premenstrual anxiety and tension, relieved when the onset of the flow indicates that she is not pregnant. Her relief will be mixed with resentment that this mark of femininity recurs.

So-called "essential" or idiopathic dysmenorrhea is the most common of all the menstrual disturbances. The true nature of dysmenorrhea continues to be a mystery. The theories are numerous, conflicting and unconvincing. Even in its minor forms dysmenorrhea, like the common cold, produces much suffering, cuts down efficiency and results in substantial economic loss. Treatment is largely unsatisfactory and cure is still more often the result of fortuitous changes in the individual's internal and external milieu.

The problem was epitomized by the experiences of a 29 year old woman who, over a period of eleven years, had become progressively more crippled by this disturbing symptom—to the point where she found it necessary to remain in bed approximately ten days each month. This patient had consulted numerous competent physicians. Ultimately hysterectomy was advised as a last resort but fortunately was refused because the patient could not accept barrenness. By this time she was taking tremendous doses of sedatives and had resorted to narcotics during the height of the menstrual colic. Psychiatric study revealed deep-seated emotional conflicts having their inception in the preadolescent period, enhanced by adolescent struggles and finally brought to fruition when she fell in love with a married man who had a large family. Years of conflict with all the frustrations inherent in the situation, highlighted by her unmarried state and childlessness, became related to and enhanced by each menstrual epoch. The dysmenorrhea became progressively more severe, each period more prolonged until the state of near invalidism was reached. The psychiatrist offered an opinion that her trouble was essentially psychic in origin and that something might be accomplished through psychotherapy, but gave a guarded prognosis. However, with intensive psychotherapy the patient showed progressive improvement and ultimately recovered to the extent that she had only slight menstrual pain lasting one or two days. Eventually she emancipated herself from her lover,

achieved a good adjustment in a healthy marriage and has since borne a child

At times dysmenorrhea does appear to be of sufficient severity to justify hysterectomy, particularly if the woman is nearing the end of her childbearing period. Even then it should not be performed without careful evaluation of the emotional factors involved, consideration being given to the possible reactions of the patient to the reality of no longer being able to bear a child. This is especially true if the woman is unmarried or although married is childless. Even though she may never achieve motherhood, as long as hope remains, despair may be avoided.

Recently one of us was called upon to examine and treat an attractive 40 year old woman, the victim of a broken home and a dominant possessive mother who had successfully thwarted her every romance. The patient had had severe dysmenorrhea for years, all varieties of treatment proving ineffectual. Finally, her physician, reasoning that she was unlikely to marry (or if she did probably would not bear children) removed the uterus. The operation precipitated a severe agitated depression requiring mental hospitalization, electroshock treatment and many subsequent psychotherapeutic sessions. Wengraf⁶ recently reported two cases of emotional illness following hysterectomy.

FRIGIDITY

Preparation for marriage, sexual life, conception and childbirth obviously begins with preparation for puberty. The gynecologist, however, is often called upon much later to correct previously engendered faulty attitudes which interfere with the consummation of marriage and its full function. In actual practice few patients consult him regarding their attitudes but come seeking relief from prevailing symptoms such as frigidity or dyspareunia which mask the basic problem.

We will have to await the companion report to Kinsey's⁷ present volume to learn the incidence of frigidity in American women in various cultural groups. Nevertheless, that frigidity is of frequent occurrence is common knowledge and a condition which both the gynecologist and psychiatrist alike find difficult to treat. Although in the early months of marriage frigidity may be times be based on faulty sexual technic, the complaint is seldom due to biological factors or structural pathology. Even when the former situation seems to be the case and the patient reports improvement following advice regarding such matters, subtle psychological forces may have been of prime importance. By the discussion of the problem with the patient, dealing with it in a realistic fashion

and giving sanction to behavior fostering added sexual stimulation, the physician often aids the patient in overcoming restrictive inhibitions. More can be accomplished by the doctor if he will take the time to discuss these matters with the woman directly rather than merely advise that she read the available literature. Many women seeking to escape from the repressions imposed by a frustrated frigid mother require much reeducation before they can overcome their inhibitions. In most instances, frigidity is, as previously suggested, a difficult problem to treat. Too many women soon resign themselves to a lifetime characterized by a more or less philosophical acceptance of their husband's advances hoping that the menopause will give them a legitimate reason to terminate honorably their almost asexual sexual lives. These are the married virgins.

In actual practice many women do not recognize and would even deny their frigidity due to ignorance of the fact that sexual intercourse for them could and should be pleasurable. Questioning will reveal that these women enjoy most forms of love-making except intercourse which they look upon as a procedure which is to provide satisfaction for the husband only. These women resent being told that they are frigid, considering themselves quite warm and affectionate. In actual fact they either accept with guilt or abandon with shame any thought of accompanying pleasure for themselves in sexual intercourse. On the other hand, there are many women who do realize their lack of satisfaction and wish to remedy the situation.

Any discussion of frigidity in women must involve a consideration of the meaning to her of the sexual act and its implications. As Lundberg and Farnham⁸ have indicated, women today are becoming "emancipated" and are enjoying greater "freedom" alongside man. There has been a decentralization of the home and concomitant changing attitudes toward children. Motherhood as such naturally cannot change but woman's orientation toward it certainly has. Sexuality likewise has not changed but woman's conscious attitudes toward its expression are much different today than yesterday. Along with the other attitudinal changes, there has come about a gradually increasing sexual awareness and activity in contrast to the former suppression and passivity. However, apparent freedom of behavior does not per se indicate a freedom from conflict (Thompson⁹) and woman attained her (sexual) freedom at considerable expense to her psychological integrity. Her unconscious was guided by a need to remain passive and to be sought after by the male but the woman was encouraged to express herself more freely in competition with him. However, her unconscious could not accept this greater freedom of expression, withdrew its support from the sexual act and the woman became frigid.

In women sexual intercourse is so intimately related to parenthood that a consideration of the symptoms accompanying the one must include a consideration of the attitudes toward the other. The woman who has intense feelings of opposition to the prospect of having children could hardly be expected to enjoy an activity the very end of which is to cause her to bear a child. On the other hand, a woman whose warm motherly instinct cries for expression will not find that sexual intercourse "leaves her cold." An example of this is the 40 year old patient who during twenty years of marriage rarely enjoyed sexual intercourse after the first month of marriage because of an intense fear of pregnancy and wish not to have children. In order to avoid relations with her husband she resorted to all sorts of subterfuge, pleading fatigue and complaining of various other physical symptoms. However, she was pregnant twice and had two daughters. A few years after marriage she began to attend various clinics seeking relief for her symptoms. Finally, when her older daughter eloped, her previous sexual conflicts were awakened and she began to suffer dyspareunia.

Frank hostility toward the marital partner is another cause for frigidity. There is the case of the 42 year old patient who, as her husband paid less and less attention to her over the years of their marriage, derived less and less enjoyment from intercourse with him. In this hysterical type of woman, demands for evidences of love and attention kept increasing with the passage of time and to her marriage had never meant more than a means of satisfying narcissistic needs. Eventually she became frankly hostile toward her husband and at that point began to suffer severe dyspareunia. Shortly afterwards she met an old acquaintance—a bachelor—who satisfied her vanity by flattery, praise and attention. She began to have intercourse with him and, rather than pain, began to experience orgasm occasionally. This case also indicates that if a woman harbors fear and hostility toward men in general as a heritage of her early environmental experiences, she may be not only frigid but suffer dyspareunia as well. Dyspareunia as a symptom may be brought about by painful contraction of the perineal musculature or the pain may represent a so-called conversion phenomenon—or both.

Psychically traumatizing events occurring at an impressionable age may warp the later life of an individual and result in much domestic frustration and suffering. An example of this was observed in a 31 year old woman who was referred for the treatment of a severe anxiety hysteria. She had been married for eight years but during that entire period, attempts at intercourse had never resulted in penetration. Each attempt by the husband to perform the act was met by resistance upon the part of the patient who claimed that even touching of the vaginal

orifice by the penis produced unbearable pain. Investigation ultimately revealed that after the death of her parents when she was quite young, the patient for some years had been raised by an older sister. This sister was married to a brutal, unfeeling husband whom the patient both feared and hated. This man would not permit his wife to go to a hospital for her deliveries but insisted that she bear her children at home attended only by a midwife. The patient, at the beginning of puberty, partially witnessed and overheard her sister during two long and painful deliveries. The association of sex and childbearing with such suffering, coupled by the fear and hatred of her brother-in-law, which was extended to include men in general, resulted in her being capable of marrying only a very passive, dependent man. He was incapable of satisfying her own deep dependency needs and was unable to stimulate her sexually. She harbored much repressed hostility toward this man which was partially projected onto his mother from whom he had not achieved emancipation. She resented his ineffectual approaches and punished him by withholding pleasure. The patient made the significant statement that if he just once had the force and courage to overcome her resistance, she probably would welcome the experience and enjoy intercourse.

In these three cases the psychological mechanisms of the frigidity and, later, of the dyspareunia were not at all masked and were readily made accessible to the patient. Much more frequently, of course, the underlying attitudes are not apparent and may even be denied by the patient. Protestations of love and affection for the husband and claims of love for children and desire for pregnancy sometimes will cause the astute examiner to wonder "Methinks she doth protest too much." Some very immature women want children—live dolls—to play with—but are incapable of genuine love and affection.

There are many other conflicts which can express themselves as frigidity and these will have to be searched for in the individual patient. In a susceptible patient such a condition may be brought about or enhanced by inept or too aggressive early sexual approaches, particularly if the hymen has remained intact and rigid. Gynecologists may frequently forestall such events by advising premarital examinations. Mothers with daughters planning marriage, who are themselves consulting the gynecologist, can be enlisted as aids to see that this type of prophylactic medicine is more frequently practiced. A woman who because of unresolved guilt feelings is unable to partake of any of the pleasures of living will embrace the sexual sphere in her anhedonia. Or, a sense of guilt over sexuality may be repressed or denied by sexual anesthesia, the frigidity then representing a denial that the act is taking place. Frigidity, at any rate, is a psychiatric problem very difficult of treatment. Probably

the chief hope is in early treatment while the newly married woman still has anxiety about the symptom and some capacity for change. After she has accepted her "lot" as inevitable and has begun to develop other means of allaying anxiety, the prognosis becomes more discouraging.

STERILITY

Robbins¹⁰ has stated "That psychiatrists should think that the emotional state of a woman influences conception would probably seem unimportant to gynecologists, were it not for its application to the widespread problem of sterility." It is well known that many women do not conceive, even though no organic basis for this disability can be found, but in certain instances a change in their life situation leads to conception. Married couples who have adopted a child may hear the prediction that they will now have one of their own. Although there is no way of proving definitely that such events are more than coincidental, there is an increasing accumulation of evidence to support the feeling that a woman at times for emotional reasons apparently may be sterile and that in such a case she will not conceive unless psychologically prepared for the event. It seems possible that the adoption in some way permits a sufficiently satisfactory solution of deep-seated resistance to childbearing.

PREGNANCY

It is generally accepted that most of the disquieting symptoms of pregnancy are founded on recognizable physiological disturbances such as hydremia, hormonal changes and other alterations in physiochemical balances. However, in all cases psychological adjustments must take place and in certain instances symptoms may stem from this source. The formation or exaggeration of symptoms frequently represents the rejection of pregnancy. Recently a 39 year old primipara, who for years had avoided pregnancy on the basis of having syphilis, conceived but for a time did not suspect pregnancy as her periods often had been irregular. Pregnancy was discovered by her physician only after she sought relief from morning nausea and vomiting of several weeks duration. Upon being told that she was pregnant the nausea and vomiting increased in severity and she developed an acute anxiety state with depression. Her condition appeared so serious that her physician discussed with her the possibility of terminating the pregnancy. The patient accepted the idea eagerly and immediately the gastrointestinal symptoms subsided. Because of her mental state she was referred for a psychiatric opinion as the need and advisability of therapeutic abortion. When the patient was confronted with the decision that her mental symptoms did not justify

the procedure there was a severe recrudescence in the physical symptomatology, necessitating hospitalization and the administration of fluids parenterally. Following careful study she was assured that there was no luetic involvement of her central nervous system and that there was little reason to fear that the child would not be normal in every respect. The nausea and vomiting subsided almost immediately and she began to think in terms of having a second child. Any unusual or unexplained symptom or symptoms complained of during pregnancy should be evaluated from the view of its possible psychological meaning to the patient. This brings up the question as to how frequently prolonged, recurrent or intractable nausea and vomiting of pregnancy may have significant psychic components.

PSEUDOCYESIS

Ruth Moulton¹¹ has pointed out that the interesting clinical picture, pseudocyesis or simulated pregnancy, has been known since the time of Hippocrates, but that little is known of the psychosomatic mechanisms involved. Although seventy-nine cases were reported between 1890 and 1899 and only twenty-six between 1930 and 1936, indicating that the condition is decreasing in frequency, our recent experience at Jefferson Hospital has shown that the condition is by no means rare. During a recent six month period, ten patients were referred to the Psychiatric Department for study.

The condition can occur at any age, Bivin and Klinger¹² collected 444 cases from the literature and found the ages to range from seven to seventy-nine. Since the physical manifestations of the condition are well known and not within the purview of this paper, they need not be enumerated. The most common etiological factors are found to be the wish for pregnancy and the fear of pregnancy. The wish of the patient for a baby may be associated with a desire to please the husband, to keep him from desertion, to have an heir, to prove her youth, to help her health, to force marriage, to get attention, to be like her mother, and so forth. As would be expected, the condition is commonly associated with other clearly recognizable psychiatric disorders such as other conversion phenomena or an actual psychosis. However, the delusion of pregnancy, unless accompanied by the physical findings ordinarily seen in pseudocyesis, should not be looked upon as representing this condition. That certain primary physical factors may play a role in pseudocyesis has been indicated by experimental work in animals. Cases with proven changes in the breast, cervix and uterus are thought by some gynecologists to be due to unrecognized spontaneous abortion with persistent corpus luteum.

The syndrome pseudocyesis, then, can be considered in two categories. The one is a simple wish fulfilment, based on the needs mentioned above. In the second group would be considered those cases in which, for one reason or another, there may be a persistent corpus luteum. Here would be included persistent corpus luteum in a nonpregnant menstrual cycle causing amenorrhea with subsequent further changes simulating pregnancy. Also in this group would be included patients who had a spontaneous abortion, probably unrecognized, with persistent corpus luteum and continuing signs of pregnancy supported by neurotic needs. The interrelationships between the two categories can only be surmised as they are unknown at this time, but undoubtedly there is much overlapping. For the furtherance of knowledge about this condition, every case of pseudocyesis should be evaluated from the endocrine, gynecologic and psychiatric points of view.

From the psychiatric point of view it is not sufficient (and, in fact, may be quite harmful) simply to inform such a patient bluntly that she is not pregnant, or that 'it is your imagination.' As in every other psychiatric condition, the removal of a symptom does not of itself benefit the personality which found it necessary to utilize the symptom. If a woman found her need for a pregnancy sufficiently great to develop a false pregnancy, it might be quite damaging to remove her supports so suddenly. Moulton states that persuasion alone 'may cause reactions of rage or depression.' Whenever possible the basic emotional problem should be investigated and treated.

MENOPAUSE

Just as the onset of puberty signals the change from girlhood to womanhood and reproduction proves her functioning capacity, the menopause indicates the end of her period of service to the species. With this frame of reference, most of the psychological and some of the physical symptoms so common at this period of life are explainable.

There are many similarities, both biological and psychological, between the menarche and the menopause. For one thing, they are both times of great endocrine change. The integration of the whole hormonal system is changed and the reciprocal relationships between various glands, such as the ovarian and pituitary, are disturbed. The nature of these and other accompanying changes would certainly appear to be sufficient to give rise to certain symptoms. These factors are discussed in the other articles in this issue.

Regardless of the physical changes, it is the psychological response to the climacterium which offers the woman her most difficult problems of

her whole life "There must be a well integrated psychological structure which can do something intelligent for the emotional needs of the individual who possesses the glands" which have now ceased functioning (Weiss and English¹²) In general, it can be said that the climacterium is one of the more severe emotional traumas which the personality must handle and it must be handled with the emotional equipment with which the woman has armed herself during her formative and productive years Her psychological response to these unalterable facts need not necessarily be pathological but frequently is

From a psychiatric standpoint, menopausal disturbances may assume various forms If the woman has had previously strong neurotic components in her personality, these may become manifested as any one of the variety of clinical psychoneuroses Frequently we see the more severe mental reaction types developing in the woman who so commonly has been a rigid, inelastic person with obsessive-compulsive tendencies causing her to be a meticulous housekeeper, a slave to convention and who is overly concerned with public opinion This person worries excessively about the small details of living and cannot go to sleep before her adolescent child is tucked in bed From the psychological aspect these character traits represent a defense against the expression of the hostile and aggressive urges which these people have found it necessary to keep buried from childhood At the time of the menopause it becomes nearer to the awareness of these individuals that they have had a lack of fulfillment in life Hostility is enhanced, guilt feelings are increased and the resulting aggression may be turned in on the self causing depression, agitation and self-depreciation—the characteristic involutional melancholia Or, the aggression may be turned outward upon the world in the form of paranoid trends—the paranoid involutional case

However, not all women having trouble at the menopause fall into the obsessive-compulsive category The woman with the neurotic character to whom puberty was an unwelcome burden, sexuality an unpleasant duty and motherhood accomplished with reluctance or else avoided altogether, may become disturbed during the involutional epoch This type of woman was usually the sexually frigid type described elsewhere She never attained a healthy relationship with her husband, and if she had a child, it was either accidental, under duress or for some other reason than the full acceptance of motherhood Such a hysteroid individual may respond to the menopausal period by an ungracious acceptance of biological facts This may be characterized by heightened irritability, mood swings, temper tantrums and vituperations against the husband for real or fancied deprivations Frequently there is also a heightened sexual excitability and increased demands for expressions of love The in-

creased sexuality, of course, is motivated by insecurity and need for self gratification rather than by mature love.

Although the physical manifestations of the endocrinological imbalance—*viz*, sweating and hot flashes—may be influenced by hormones, obviously the mental reactions cannot be materially altered by this type of therapy. If the patient is troubled by anxiety, fatigue, insomnia, early morning awakening and depression which tends to diminish later in the day, if there is indecisiveness, lack of ability to concentrate, self depreciation and a general loss of pleasurable appetites, these symptoms, being predominantly psychological in nature, can hardly be expected to respond to hormonal therapy alone. Too often patients presenting these or allied complaints are treated month after month with injections of a hormonal substance which usually is of little value aside from the psychotherapeutic benefit derived from the associated reassurance, support and suggestion. The best results are achieved by the physician who through intuition or training can take a warm and sincere interest in the patient's personal problems. A fair percentage of these patients require the help of a physician trained in psychotherapy, and some are sufficiently ill to necessitate the use of more drastic treatment such as electroshock therapy. Although the prognosis is generally favorable in the majority of cases, none is easy to treat because of the fixity of the personality pattern. Some do not respond to any type of therapy and become chronic invalids. Here, as elsewhere in psychiatry, classification is of minor importance compared to the need for an understanding of the emotional conflicts involved, so that every available method of approach can be utilized, whether a simple environmental readjustment or an attempt at a more complete reorganization of the individual's personality.

THERAPY

Much that has been said certainly will not be new to the observant gynecologist. As a matter of fact, for years he may have recognized the psychic factors in the various symptoms of which his patients complained, but may have found that recognition and cure are not synonymous. Therapy with these patients is difficult, frequently long and all too often the results are not gratifying. The menopausal patient, for instance, is particularly difficult because little can be offered to her as far as reliving part of her life is concerned—biology cannot be reversed. The frigid woman is frequently discouraging to treat because the psychological conflicts upon which the symptom is based usually stem almost from the roots of the personality and require a rather fundamental reorganization of basic attitudes. It is not our intention to imply that these are

hopeless situations, they are far from that. We do feel, however, that anyone dealing with these patients should have a full understanding of the problem so that he will not lose his perspective and so that he will avoid discouraging the patient by ill-advised encouragements and promises of rapid cure.

This brings us to the first point to be remembered in dealing with any patient whose symptoms will have to be viewed, at least in part, with a psychologic frame of reference (Rennie¹⁴) The patient should be able to leave the doctor's office with the feeling that he understands something but not everything about her and her emotional problem and is prepared to do everything to help. This means that the doctor will have gotten across to the patient that he understands how much her symptoms—psychic or otherwise—bother her and how much they interfere with her daily life and happiness. This is an important point and means that the doctor has not given the impression of understanding all about the symptom and its relief. Such an attitude leads the patient to work further with the doctor to find out about her difficulty rather than become passive, believing that the doctor "knows it all" and will cure her. Usually after relating a symptom and answering a few routine questions about it, the patient will ask "Well, what's the matter with me, Doctor?" The ready answer is the easiest, of course, and the patient might be informed then that she probably has a retroverted uterus, or a cervical cyst or that "it's your nerves." Such answers obviously do not call for any further response from the patient (Rogers¹⁵) On the other hand, if the doctor shows his interest and understanding and also his honesty by some such remark as "I don't know, but these cramps seem to make you pretty uncomfortable," then the patient may begin a discussion of what her symptoms have done to her in everyday life. The patient may even begin to accompany her history-giving with more overt emotion. When a patient expresses feeling in an interview, she provides the lever for psychological reconstruction.

An important thing which should be understood when dealing with emotional problems is that an understanding of the mechanisms which are at work within the patient's personality is of the same order of importance as the knowledge of pathology in physical disease. It helps the doctor to know what is going on, influences therapy and also makes his own work far more interesting. However, a patient will not recover from pneumonia because of the doctor's or the patient's knowledge of the pathology. Likewise, a patient with neurotic symptoms will not recover because the doctor has told her all of the dynamics of her illness as he views them. Every doctor can learn this for himself easily by informing a

patient of the apparent mechanisms of certain symptoms and then observing that the symptoms remain unchanged These are emotional illnesses and require emotional therapy

Therapy depends on the emotional relationship between the therapist and patient which fosters growth in the direction of maturity and therefore cannot be based on an appeal to reason Were this not true, any intelligent patient with a neurosis could read a book on the subject and effect a cure for himself Any psychiatrist who has had patients come to him for therapy after having read one or more of the popular books on how to cure one's own emotional troubles, can attest that reading as such is never curative We do not deny that there are many people who are benefited by bibliotherapy The improvement in such an instance is probably brought about chiefly by the accompanying reassurance that others have similar difficulties The aloneness so typical of the neurotic is diffused and dissipated

Just as it is unwise to rationalize with a patient regarding his symptoms, it is useless to moralize A moralistic attitude toward patients symptoms and difficulties will be apt to engender feelings of hostility and, in turn, further increase feelings of guilt A few words about guilt feelings would be in order here since the term is used so frequently When we speak of guilt feelings in relation to symptoms we do not mean realistic, well founded feelings of guilt, such as an individual might have if he stole some money We do mean the unrealistic phantasy founded guilt feelings such as cause a mother to grant a child a special favor immediately after punishing him proportionately and justly for a real wrong-doing In brief, then, a moralistic approach to the patient is a poor therapeutic approach It seldom solves the difficulty and may even increase the conflict

Patients will ask frequently for advice or direction on personal problems Here again the therapist should function as a catalyst in helping the patient to form her own decision and should not offer his personalized opinions or advice At times, of course, statements of scientific fact regarding specific treatment, such as x ray, radium or hormonal therapy are necessary However, statements such as 'I think you should or, If I were you, I would and the like have no place in psychiatric therapy By such a statement the physician has set himself up as an authority on the patient's personal problem Since the opinion has been given by an authority the patient may act on it for that reason alone rather than because it is a wise course to follow Or, a patient who has always had difficulty accepting authority may reject even the correct course of action, primarily because it has been suggested by a hated authority symbol

SUMMARY

1 Many, if not all, patients presenting themselves to gynecologists have an emotional component to their complaints. The primary etiological importance of the psychological factors can be graded from zero—in such a condition as carcinoma of the fundus—to almost 100 per cent in frigidity.

2 The doctor is not doing justice to his patients if he does not partake in or secure emotional therapy for these patients.

3 Many of the conditions such as dysmenorrhea, frigidity and dyspareunia are but symptoms which are the compositions of our culture reflected by the sounding board of a poorly adjusted personality. They are played on the particular instrument of that individual's heritage in the key of her past environmental influences.

4 Pseudocyesis is an interesting condition by no means rare or fully understood and warrants further gynecologic, endocrinologic and psychiatric investigation.

5 Menopause is a particular problem in which organic changes and psychological stresses each give rise to particular symptoms. Since the organic changes are quite universally the same, the variability of symptoms is best accounted for by different psychological forces within the personality.

6 Treatment of these conditions is often difficult, usually tedious and at times discouraging, particularly if the physician loses interest. But in a substantial percentage of cases with appropriate and adequate psychotherapy, the results are most gratifying.

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THE RATIONAL MANAGEMENT OF LEUKORRHEA

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LEUKORRHEA is a term used to describe an abnormal discharge from the genital tract of the human female and is probably the most common complaint of gynecological origin. The discharge may vary in color, consistency and content, and is usually referred to by the medically untrained as leukorrhea when it originates from the genital tract regardless of cause. Needless to say, a consciousness by the individual of a constant secretion from the genital tract is abnormal and should be investigated and treated as is necessary.

This presentation will discuss leukorrhea as a discharge from the genital tract of the human female after puberty which is primarily annoying to the individual and which has no serious organic basis for its cause. I shall not consider the discharges caused by obvious and often extensive ulcerative lesions of the vagina and cervix such as cancer, tuberculosis and the various granulomas, nor those caused by acute gonorrhoea.

The most common types of leukorrhea without an organic basis may be grouped in two classes, namely:

- 1 Simple hypersecretions from the genital tract with normal vaginal flora and biology
- 2 Hypersecretions from the genital tract with abnormal vaginal flora and abnormal biology

NORMAL VAGINAL BIOLOGY†

If we accept this classification of leukorrhea or vaginal discharge, we must have an appreciation of the structure and physiology of the lower genital tract. The vaginal canal is lined by a membrane which extends from its introitus to its insertion at the external os of the cervix. The vaginal membrane is a fibromuscular structure which is pliable for most of its area and is fixed rather firmly to the cervix of the uterus. Usually the anterior and posterior vaginal walls lie approximated and no cavity exists except about the cervix and, therefore, the capacity of the vagina for secretion is quite small. The vaginal membrane is covered by a dense

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† The term "biology" as used here refers to the various physiological, bacterial and chemical phenomena which occur in the lower genital tract of the female.

surface of squamous epithelium which normally extends throughout its length and ends symmetrically about the external os of the cervix. In the prone position, the so-called Sims' position, or the knee-chest position the vagina will become dilated and capacious normally. Vaginal epithelium has a high glycogen content and, through enzymatic action and the action of the normal bacterial flora of the vagina, the glycogen of the epithelium is converted into lactic acid which is the normal acidulating factor of normal vaginal secretion.

Normal vaginal secretion has an acidity with a pH near 4.5. It varies somewhat depending upon the location in the vagina from which it is secured and upon the time of the menstrual cycle at which it is taken. The source of the vaginal secretion is not entirely understood since there are no glands in the normal vaginal membrane capable of secreting the liquid. We can, however, assume that normally the cervical mucus is deposited into the vagina and perhaps some more of the vaginal moisture is derived from disintegration of the desquamated epithelium. Certainly the cervical mucus is not alone responsible for vaginal moisture because normal vaginal moisture exists after complete hysterectomy.

The normal bacterial flora of the vagina is the lactobacillus of Döderlein. It is a large gram-positive organism closely associated with the acidophilus bacillus and can easily be identified by simple staining methods.

APPRAISAL OF VAGINAL SECRETION

When the symptom of leukorrhea is present one must consider the amount, appearance and composition of the normal vaginal secretion. A normal secretion is just enough in amount to produce moistening of the external genitals without soiling the clothing, but it should be understood that at certain times of the menstrual cycle, especially during the ovulatory period and just before cyclic bleeding begins, many women normally will notice some excess of secretion. The appearance of the normal vaginal secretion is characteristic. It is flaky, somewhat crumbly or granular, and grayish white or pearl colored. The composition of the normal material consists of desquamated epithelium, various amounts of glycogen, but largely aciduric bacilli. These elements can be recognized by simple methylene blue or Gram staining which will demonstrate the epithelium as flat and large cells, and many large rod-shaped bacilli which are gram-positive. The use of iodine vapor is a simple means of demonstrating the glycogen factor in the epithelium. It reacts with the glycogen in the cell to produce a brownish color reaction in the moist and freshly treated smears. The acid reaction of the material can be determined most easily by the use of litmus paper. For scientific work an electric potentiometer will add interest to one's observations.

These descriptions of the physiology and anatomy of the genitals are characteristic of woman during the procreative period of her life but do not apply during the period before puberty and after the climacteric. These characteristics are probably maintained by normal anatomy and the normal physiology is maintained by certain endocrine balances of the individual.

SIMPLE HYPERSECRETION FROM THE CERVIX

An approach to the problem of management of leukorrhea is based upon a carefully taken history, a thorough examination and a special consideration of any findings which vary from the normal. We cannot classify categorically the various causes of these discharges but most of the patients with normal vaginal flora and biology will fall into two groups.

In the first group are the individuals who have complained of a discharge since the establishment of the menarche. Many of these individuals are virgins while others have had coitus but no pregnancies and no history or evidence of genital infections.

A careful history of these patients will indicate that the discharge began when the menses were established and that it has persisted since that time. Quite frequently one of these patients will make the statement that the condition has been caused by a 'weakness of the individual,' and often various types of systemic treatments or douches have been prescribed.

These patients have a simple hypersecretion from the genital tract. The vaginal flora, the vaginal acidity and the glycogen in the vagina are normal, and the vaginal membrane has a normal appearance except about the external cervical os. About the external cervical os there is an area variously referred to as a congenital eversion, erosion or ulcer, but which I prefer to call *heteroplastic cervical tissue*, since 'heteroplasia' best describes the formation of normal tissues in an abnormal location. These areas of eversion are usually congenital in origin and because this heteroplastic endocervical tissue is being exposed to the acid secretion of the vagina, it is probably stimulated to produce an abnormal amount of mucus. If the condition is allowed to go untreated, a cervicitis will develop and extensive changes may occur in the whole cervix. This concept is tenable on the basis that an acid environment is abnormal for the alkaline secreting endocervical tissue.

Leukorrhea in the female who has a congenital eversion of the cervix can be treated successfully by the destruction of the heteroplastic endocervical tissue after the condition has been recognized from the history and examination of the patient. Examination of the virginal patient can

be accomplished in many instances without pain and without rupturing the hymen if care is exercised and if skill has been acquired in the use of small and suitable instruments In a few instances, however, the virginal patient should be examined and treated under anesthesia Examination and treatment of females who are not virginal can almost always be managed without anesthesia

Closely associated with the discharges in the virginal and nulliparous female are the ones observed after pregnancy In this group of patients, the medical history will indicate that the discharge began after the pregnancy and has persisted since that time When the vaginal secretion is studied, very slight or no changes from the normal will be observed The acidity, the cell content and the flora of the vagina will correspond to what has been described as normal, and the color and appearance of the lower genital tract will show no unusual changes However, the amount of secretion will be excessive Examination of the cervices of these women will usually show changes described as cervical tears which have been induced by the trauma of labor and delivery The delivery will usually have been rapid, with evulsion of the cervix during its course, or it will have been an exceptionally difficult and traumatic delivery after a long and tedious labor It is interesting to deduct from the appearance of the cervix the kind of a labor which the patient experienced and it is amazing how often one can be correct in one's conclusion

These statements suggest a conclusion about cervical eversions and erosion which seems to me extremely pertinent My own studies, which include careful clinical observation of a great many patients over a period of many years, convinces me that most eversions of the cervix are *congenital in origin*, that in a normal labor and delivery the cervix is not traumatized, and that previously treated eversions in most instances do not recur These conclusions are based on the appearance of previously treated cervices after normal deliveries Many times I have treated the cervix of a nulliparous or virginal woman with a *congenital eversion of the cervix* by destroying the heteroplastic endocervical tissue These same women have been observed following normal labors and deliveries and no eversion has recurred, the cervix having remained normal or as it was before delivery It would seem that our past concepts have been based on conclusions drawn from practices which have changed considerably in the past few decades We are now observing patients and making genital examinations before marriage and at the beginning of pregnancy, and I think we have learned from these observations that *congenital evasions of the cervix are common* and are the most common cause of the noninfectious types of leukorrhea

Destruction of the heteroplastic or misplaced endocervical tissue may

be stated categorically to be the proper treatment of leukorrhea in almost every instance where there is no change in vaginal biology or where infection plays no part in its cause I shall describe later a technic which is effectual in destroying misplaced endocervical tissue

LEUKORRHEA CAUSED BY CHANGED VAGINAL FLORA AND BIOLOGY

There is much controversy as to the cause for the discharges in patients with a changed vaginal biology and one cannot be categorical in discussing them. The vestibule of the vagina is usually hyperemic in appearance and some of the tabs of tissue about the genitals may be reddened. The secretion from the vagina varies in color from the normal to a dark brown or yellowish tinge. It is thin in consistency and when examined microscopically without stain will be seen to contain many pus cells and the *Trichomonas vaginalis*. When it is stained, many types of organisms will be apparent. The chemical reaction of the secretion will vary from the normal either to the alkaline or acid side. Most often it will be alkaline. In many instances the glycogen content of the desquamated epithelium will be less. The vaginal membrane shows an inflammatory reaction with many petechia like areas about its fixed portion. There will be some weeping of the vaginal membrane after the secretion has been wiped from it. Often the whole vaginal membrane appears as an intensely inflamed structure. This condition has been variously referred to as nonspecific vaginitis and *Trichomonas vaginalis* vaginitis. Many observers believe that the condition is caused by the *Trichomonas vaginalis* because it is so frequently observed in the secretion. The common and important characteristics of these discharges, it would seem, are the facts that the chemical reaction, the bacterial flora and the genital biology has changed from what we consider normal.

From a practical clinical standpoint we must look for factors in the history and our examination that might account for these changes from the normal vaginal biology. Often one will observe focal areas of infection in the lower genital tract or some endocrine imbalance.

Focal Areas of Infection in the Lower Genital Tract.—The focal areas of infection in the lower genital tract can be recognized by examining the secretion from the tubules about the urethra and the ducts of Bartholin's glands for exudate or pus cells. Evidence of focal infection of the cervix can be secured by inspecting the cervix carefully and finding nabothian cysts, ectropions, deformities, eversions and granulations in the cervical canal and abnormalities in the cervical secretion. Normal cervical secretion changes somewhat in consistency throughout the menstrual cycle but usually it is clear in color and contains only an occasional pus cell. All variants from this observation may be considered as abnormal. If

cervical secretion contains many pus cells and bacteria, it indicates to me that a focal area of infection is present in the cervix

If focal areas of infection are present in the lower genital tract they should be treated by drainage or destruction. If means for destruction of these focal areas are not available, sulfonamides or antibiotics may be tried but in my experience they have not been entirely reliable and I depend almost entirely upon drainage or destruction to effect their resolution. In most instances no further treatment will be necessary.

SENILO VAGINITIS

The so-called trophic or senile vaginitis has been recognized as the cause for discharges in individuals who have been castrated or in women past the menopause. It is recognized rather easily by the thin pliable vaginal membrane with large various sized areas from which the epithelium has been desquamated. Sometimes there is a history of pain and discomfort and some bleeding at coitus or when an effort is made to take a douche. The normal vaginal flora will be absent and the vaginal biology will have changed. The ulceration of these areas should be studied by biopsy for malignant changes. In some instances I have observed extensive adhesions or synechiae of the vaginal walls and on one occasion almost complete occlusion of the vaginal canal.

To control the simpler manifestations of this condition, an attempt should be made to change the chemical reaction of the vagina. This can be accomplished by the use of an acid douche such as acetic acid or lactic acid. A good treatment would consist of 1 tablespoonful of vinegar to 2 quarts of water or 1 tablespoonful of U.S.P. lactic acid to 2 quarts of water. Another method of symptomatic relief consists in using a solution of 2 drams of beta lactose to 1 pint of water as a simple vaginal instillation. Stilbestrol or estrogen, or one of the substitutes, can be used cautiously but is not recommended except in the extreme or rare cases and then only with very careful and periodic observation of the patient.

MISCELLANEOUS TYPES

Most leukorrheal discharges will be recognized as caused by the processes discussed previously in this presentation. There are, however, a few instances where these concepts cannot be applied and indeed there are some cases which seem to be intractable. Endocrine imbalance with thyroid, estrogen or other deficiency may account for a few of them. The collection of urine in the vagina after micturition conceivably can be responsible for some of them. Hyperacid secretion in the vagina with yeast fungus infestation as a cause for leukorrhea in pregnancy is common.

and is sometimes seen in diabetes in the nonpregnant individual. Some of these conditions are caused by factors which are not understood and many complicated procedures have been recommended for treatment. In my own experience topical applications, douches and antiseptic powders have been of little value in the management of these patients except to give them symptomatic relief. My approach to the problem has been to determine the cause for the discharge and when that is determined the treatment seems quite easy and successful. When the cause cannot be determined, repeated review of the history and examination may disclose factors which have previously been overlooked.

THE TREATMENT OF LEUKORRHEA

Leukorrhea in my experience has been most successfully managed by first carefully studying the discharge and then by destruction of any recognized areas of heteroplasia or focal areas of infection about the lower genital tract. This can be accomplished in the office with the proper appliances and the acquisition of skill in their use. The necessary appliances for these procedures as I use them consist of good light, small probes for locating the glands and tubules about the urethra, a tissue coagulating machine with proper electrodes which will fit into the tubules and glands about the urethra, and electrodes which can be used for the destruction of the heteroplastic endocervical tissue about the external os of the cervix. When the glands and tubules about the urethra are coagulated, anesthesia is induced by the application of 10 per cent cocaine solution with a cotton wrapped applicator placed in the urethral canal for a few minutes. There are usually two tubules just outside the external urinary meatus known as Skene's tubules and just inside the external urinary meatus there are other tubules which can be recognized. The electrode is inserted into these tubules and coagulation is completed in about one second by a properly adjusted appliance. The purpose of this procedure is to destroy the epithelium lining the canal of these tubules and when healing is complete the tubule is found to be destroyed.

For destruction of heteroplastic endocervical tissue about the portio of the cervix, I use a coagulating electrode of a diathermy machine. No anesthesia is usually necessary. The whole area of heteroplastic tissue about the external os of the cervix is coagulated and some of the area lining the external os of the cervix is treated. This procedure must be executed in such a manner that the glands are destroyed without injury to the underlying tissue of the cervix. Care must be taken to avoid excessive scar formation about the cervix after healing has occurred. If the cervix is badly deformed with cysts and considerable inflammatory changes with edema and enlargement of the cervix, an endocervical

resection should be done. These procedures should never be accomplished without careful study to exclude an early malignancy. Whenever there is the slightest suspicion of ulceration, a complete cervical biopsy should be taken before treatment is undertaken. When cervical biopsy and endocervical resection is indicated, I always admit the patient to the hospital, where facilities are available, for complete study and adequate and extensive treatment.

After coagulation of the cervix, healing occurs over a period of about four weeks and when completed the entire area of destroyed endocervical tissue becomes replaced with squamous epithelium without contracture or deformity. While healing from this treatment is occurring, I have the patient use at low pressure a simple mildly antiseptic douche of a 1:4000 zephiran solution as necessary. This is prepared by using 1 teaspoonful of concentrated zephiran, 12.8 per cent, to 2 quarts of warm water. Immediately after the treatment the patient will experience a profuse foul-smelling vaginal discharge, and frequently from the seventh to the tenth day after treatment some bleeding will occur. This may occasionally become severe enough to necessitate vaginal packing for its control. If this procedure is done correctly, the endocervical tissue should be completely destroyed. There should be no contraction or deformity of the cervix and the progress of subsequent labors should not be impaired. The whole coagulated area should have the appearance of a normal cervix with slight blanching of treated surfaces which may persist for some time. The secretion from the cervix will become normal in amount and its appearance will be clear in color and normal in consistency. The vaginal biology will become normal.

Most cases of leukorrhea will be cured by this type of management and no other treatment will be necessary. In some instances the patient will complain of a leukorrheal discharge after this treatment and much ingenuity must often be exercised in its control. Douches and applications to the vaginal canal may be used. It is my practice to use acid douches and jellies with the idea of developing, by substitution therapy, normal vaginal acidity. To avoid contamination of the lower vaginal canal with the flora of the external skin about the genitals, I have the patient use a mildly antiseptic soap for bathing about the genitals and the axilla. Neko soap, 1 per cent, made by Parke, Davis & Company, is easily available and very satisfactory for this purpose.

In leukorrheal discharges in which the vaginal secretion is hyperacid the yeast fungus may often be demonstrated. A rational and effective management consists in the use of 1 per cent sodium perborate solution to overcome the hyperacidity.

Topical application of antiseptics to the genital canal will inhibit the

natural mechanism which maintains normal vaginal biology, consequently their use has never impressed me as being a logical method of managing vaginal discharges.

TRICHOMONAS VAGINALIS VAGINITIS

I have mentioned that the *Trichomonas vaginalis* is a common and easily recognized organism observed frequently when the vaginal secretion is not normal and an associated vaginitis is present. In omitting a discussion of this problem as an entity I do not wish to be pedantic or confusing, and I think the omission should be explained. The *Trichomonas vaginalis* has been much discussed in the literature and has been cited and accepted by many observers as a cause of vaginitis. There are, however, some of us who do not agree that this particular organism is responsible for the condition when many other less easily recognized organisms could be equally responsible. It is my considered opinion that the *Trichomonas vaginalis* is commonly observed in the vagina of women with abnormal vaginal flora when the chemical reaction of the secretion has changed toward the alkaline side. In the management of this condition it seems to me best to direct one's efforts to the development of an acid vaginal secretion. This can usually be accomplished if attention is directed to the principles outlined previously in this presentation.

SUMMARY AND CONCLUSIONS

In this presentation I have emphasized the importance of normal vaginal flora and normal vaginal biology. I have not used the term "vaginal mucosa" for the reason that the vagina is covered, not by a mucous membrane, but by a special type structure which is more accurately called the vaginal membrane or vaginal epithelium. I have also used the term, "heteroplastic endocervical tissue," to describe the misplaced endocervical tissue which appears on the portio of the cervix.

Throughout I have emphasized the importance of being able to recognize the normal vaginal biology and how variations from the normal may cause the symptom of leukorrhea.

The leukorrheal disorders which I have discussed and which are the ones most commonly observed are, first, the normal but excessive vaginal secretion with congenital or acquired organic changes in the cervix, and, second, the excessive and abnormal vaginal secretion which is induced by focal areas of infection in the glands of the lower genital tract which includes the cervix. There is also a group of patients who probably have some endocrine imbalance.

Most leukorrheal discharges when not caused by serious organic dis-

ease can be cured by properly treating the cervix and destroying other focal areas of infection in the lower genital tract I have described a method which I use as an office procedure Some leukorrheal discharges are caused by conditions not understood and which may be an endocrine imbalance These I do not feel competent to discuss at the time

In the usual case of leukorrhea douches and local medicaments give only symptomatic and temporary relief When used they should be employed as substitutive therapy, to create a condition as near to 'normal as possible For this reason a full appreciation of their properties and actions is necessary

THE SIGNIFICANCE OF CYSTIC ENLARGEMENT OF THE OVARY WITH RESPECT TO TREATMENT

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Cystic collections of fluid, in general, may arise either by the obstructive accumulation of the secretions of normal cells, or from the secretions of liquefaction necrosis of neoplastic cells. In either case, cystectomy is the expedient course. A cystic gland is more simply treated by removal than by an attempt to relieve duct obstruction. Cystic neoplasms progress in size, and eventually produce symptoms due to torsion, degeneration, mechanical pressure, or interference with the function of the host organ. Malignant change is a dangerous possibility in any cystoma, but especially in those of the ovary, 15 per cent of which are malignant.

Normal ovarian function entails the formation of a cyst, the Graafian follicle. Usually the cyst is single, grows in an orderly fashion to about 5 to 10 mm. in diameter, ruptures to release a mature ovum, and thereafter a corpus luteum develops from its collapsed walls. This process does not produce palpable enlargement of the ovary, and is not ordinarily accompanied by disturbing pelvic symptoms. Under some circumstances this course of events may be perverted and arrested, usually at the preovulatory stage. Single or multiple oversized follicles, or an enlarged corpus luteum containing fluid, may develop and persist. These perversions of the follicle apparatus may be very common as accidental physiologic variants. Ovaries bearing these structures are enlarged to a variable degree, but usually to not more than 5 cm. in diameter. These are the 'non neoplastic' or 'physiologic' cysts of the ovary. The management of these cysts involves (a) their differentiation from young cystomas, and (b) treatment, where necessary, to remove etiologic factors and to offset symptoms due to the ovarian changes.

PATHOLOGY

On gross examination the ovarian enlargement is most commonly due to the presence of many cysts varying from buckshot to cherrystone size (follicular cystosis, cystic degeneration of the ovary, sclero-cystic ovaries, multiple follicular cysts, polycystic ovaries). These cysts may be scattered through the ovarian parenchyma, but tend to crowd the cortex.

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opposite the hilum. Sometimes the ovarian surface is studded with thin walled translucent cysts (Fig 194), a type more common near the meno-



Fig 194.—Multiple cysts in a premenopausal ovary



Fig 195.—Histologic section showing cysts without distortion of the ovarian contour

pause. In other cases there is no distortion of the ovarian contour, and the ovarian enlargement is produced by many cysts lying subjacent to a bluish-white thickened ovarian capsule (Fig 195). The surface fissuring

is lost, and the capsule is smooth and pearly white, with scattered telan giectatic capillaries.¹⁰ These changes tend to occur bilaterally, although the process may be much more advanced on one side. The gross enlargement seldom exceeds the size of a plum. In another form, the ovarian enlargement is mainly due to a single large cyst (hydrops folliculi) which may be associated with multiple cysts in the same or opposite ovary (Fig. 196). The origins and significance of these varieties are probably alike, at any rate, the lesions are clinically undistinguishable and must be handled as one.



Fig. 196.—Hydrops folliculi.

On cut surface the ovarian capsule is thickened and white. The cysts have smooth nonpapillated walls, and contain a clear straw-colored, or occasionally a hemorrhagic fluid. The ovarian stroma is moist and edematous, and may bulge as the ovary is hemisectioned, because of increased intracapsular pressure. Edema and fibrosis are accentuated when the condition is of long standing. In some cases a boggy, edematous enlargement overshadows the cystic change ('oyster ovaries'). Usually there is lengthening of the ovarian ligament, with some prolapse of the ovary. Varicose veins in the broad and infundibulopelvic ligaments are common, and uterine retrodisplacement may be associated.

On histologic examination, congestion, edema and fibrosis of the stroma and 'cirrhosis' of the ovarian tunic are found. Compression of the stroma cells may be apparent.¹¹ The cysts show the changes of follicle atresia. The ovum has disappeared, and the granulosa lining may be well preserved, be thinned out, or may disappear entirely leaving a theca cell lining. When there is no recognizable granulosa, the designation 'simple cyst' is used, since it is no longer possible to indicate its origin from a

follicle rather than a small serous cystadenoma.¹⁶ The theca interna may be luteinized.^{19 25 28} In many cysts the fluid is empty of hormone content¹⁰ but in some instances estrogenic activity is apparent. The endocrine activity of these cysts depends on the quality of the cells lining the cysts, a factor which may differ from cyst to cyst and from time to time. Some cysts are undoubtedly capable of producing significant amounts of estrogen,^{27, 32} but not if the granulosa lining is lost.¹¹ Progesterone may be produced by a luteinized granulosa or theca interna, and secretory changes in the endometrium may result, even in the absence of a post-ovulatory corpus luteum.²⁵

A corpus luteum cyst may arise from an accidentally excessive hemorrhage into the normal corpus luteum. The blood is slowly resorbed, leaving a straw-colored fluid content. The lutein wall persists, and continues to secrete estrogen and progesterone, apparently only because of the distention. These cysts are not common. They arise abruptly and are unilateral.

ETIOLOGY

Inflammation—Formerly ovarian cystosis was believed to be an inflammatory-degenerative process. Acute bacterial inflammation in the pelvic organs can give rise to diffuse oophoritis, with thickening of the ovarian capsule and adhesion to surrounding structures. Such a condition is encountered after gonorrhreal and other types of pelvic peritonitis. Cysts develop either because of the altered endocrine responsiveness of the inflamed ovary, or because of simple mechanical interference with follicle rupture. In the absence of gross evidence of pelvic inflammation, it is doubtful that bacterial invasion accounts for many cases of ovarian cystosis.

Mechanical Factors—Local factors affecting ovarian dynamics may have an important role. Ovarian prolapse with passive congestion and edema can result in cellular embarrassment and alter the pattern of Graafian follicle growth. Weed and Collins have produced experimental ovarian prolapse in dogs, by suturing the ovary to the anterior parietal peritoneum. These ovaries develop follicular cysts histologically similar to those found in humans. Clinically, uterine retroversion and ovarian prolapse are often, but not always, followed by cystic enlargement of the ovaries. Weed and Collins³³ feel that dependent prolapse of the ovaries is the common and adequate etiologic background for cystosis.³³ They state "By an obscure mechanism, young ovaries associated with mild developmental anomalies, such as retrodisplacement of the uterus with prolonged and lax ligaments, respond to a normal hormonal stimulus with pro-

longed vascular congestion, and varicosities in the supporting ligaments. The ovarian weight increases and the dependent position is more pronounced. Interstitial edema increases and the nutrition of the growing follicle is impaired. Follicles grow from the primordial to the vesicular stage, but the ovum loses viability because of poor nutrition, and the follicle becomes atretic. Because no corpus luteum is produced, irregular and continuous follicular growth is fostered by the normal activity of the anterior pituitary gland without the inhibitory effect of a corpus luteum." One might question this theory on the grounds that uterine retrodisplacement alone does not invariably result in cystosis, and secondly, that this concept does not explain the strong tendency for spontaneous disappearance of these cysts. Whether or not a minor developmental laxity of ligaments originates the condition, prolapse is certainly a common manifestation secondary to the increased size and weight of the ovary. As such, it may accentuate and perpetuate the process by the mechanism outlined above.

Hormonal Factors—Since normal follicle maturation and rupture is governed by hormonal stimuli, alteration of these stimuli, as well as changes in ovarian responsiveness, can be the source of cystosis. Normally a pituitary gonadotrope excites growth in a large number of primordial follicles, of which usually only one continues to maturity. The influence that arrests development of the other follicles and causes their degeneration (follicle atresia) is unknown. It is probably hormonal rather than locally mechanical, since ovulation does not occur in the opposite ovary. A special factor governing follicle atresia could originate in the most rapidly growing follicle, elsewhere in the ovary, or in the pituitary gland. The absence of such a principle would account for the persistence of follicle cysts in varying stages of development.

The mechanism of follicle rupture at maturity is also unknown. It is argued that follicle cysts may accumulate when a thickened ovarian tunic, or an ovarian cortex crowded with older cysts obstructs the surface rupture of a growing follicle.⁷ However, since rapid growth of oversize follicles occurs following the release of large quantities of gonadotropin from a hydatid mole or chorionepithelioma, or after administration of large amounts of chorionic gonadotropin,⁸ it seems unlikely that rupture of a follicle depends on mechanical factors alone. Liberation of an ovum follows a quiet opening of the follicle wall⁹ at the point where progressive cellular changes have taken place under adequate stimuli.¹⁰ It is therefore logical to suppose that a perversion of the unknown relationship between hormone stimuli and follicle accounts for the development of multiple immature follicles.

In some situations exaggeration of gonadotropic stimulation is apparent. In patients with hypertrophic changes in the anterior pituitary body, Kraus found a high prolan level and cystic degeneration of the ovaries in many instances.¹³ Ordinarily gonadotropin assays do not show any change, either because the pituitary shift is small or of a type not demonstrable by current methods. Robinson believes that in ovarian hyperfunction with cystosis (and with excessive uterine bleeding) the follicular apparatus is overstimulated by an increase of prolactin A. There is an associated stimulation of the thyroid, which results in reduction of prolactin B production, and increased vagotonia, which augments prolactin A secretion. In ovarian hypofunction with cystosis (and with reduced uterine bleeding) prolactin B secretion is increased and continuous, with excessive adrenal secretion and sympathetic tonus, resulting in pronounced luteinization of the follicular cysts.¹⁹ The pituitary fault might derive from psychic or metabolic derangements affecting the hypothalamus.

In other instances it seems that a defective ovarian response is important. Immature ovaries in fetuses near term or newborn babies²³ or at puberty, the aging ovaries of the menopause, or fragments of ovarian tissue left after extensive operations are all likely to exhibit cystosis (Fig. 197).

Whatever may be the initial hormonal imbalance, ovarian cysts lined by granulosa or theca lutein cells are the outcome. Sustained estrogen or progesterone secretion by these cells can result in back effects on the pituitary and eventuate in a fixed endocrine imbalance. Stability is probably unusual, and the glandular defect, pituitary or ovarian, is ordinarily transient and self-correcting.

The cause for persistence of a normal corpus luteum or a corpus luteum cyst is obscure. While tremendous doses of chorionic gonadotropin can prolong the activity of lutein cells,⁴ it is improbable that similar degrees of luteotropic stimulation occur naturally. Persistent lutein cell activity inhibits production of follicle-stimulating gonadotropins, and new follicles do not appear.

DIAGNOSIS

Clinical differentiation of the non-neoplastic cyst from a true cystoma is difficult, but the presumptive evidence is adequate. Neoplastic cysts are usually unilateral when young, constantly enlarge, and in their early stages do not affect the menstrual cycle or give rise to any symptoms at all. Non-neoplastic cysts are frequently bilateral, and may decrease in size from time to time, almost never exceeding 5 cm. in diameter. While they are often asymptomatic, there may be associated minor menstrual disturbances.

When a small ovarian cyst is detected on pelvic examination, the probability of its "physiologic origin is overwhelming. In a survey of ovarian cysts removed by operation, Cooke found that 99.1 per cent of lesions under 5 cm were retention cysts.⁵ Of 461 small ovarian tumors (including 384 not treated surgically), 447, or 96.9 per cent, were non neoplastic in a series studied by Miller and Willson.⁶ Since most patients with cysts escape hospitalization, the preponderance of functional cysts is probably greater than these figures indicate.

The risk of delay in treatment of an early ovarian malignancy is very small. In Cooke's series of 1878 cases of cysts less than 7.5 cm in diameter, malignancy did not occur. In Miller and Willson's series of 461 cases, fifteen were neoplastic of which three proved to be malignant. This fact could hardly warrant prompt prophylactic oophorectomy on the other 446 women, but it does denote the need for careful and repeated pelvic examination whenever an ovarian enlargement has been found. If the ovarian mass steadily enlarges, laparotomy is warranted. A few weeks of preliminary observation are not likely to sacrifice a favorable outcome in an early neoplastic lesion. Laparotomy by wholesale is not an acceptable alternative.

SYMPTOMS

Non neoplastic cysts are capable of producing symptoms, the relief of which is the only rationale for treatment. Symptoms can arise from local organic changes in the ovary, or may depend on altered hormone production.

Pain—Bilateral lower pain, deep and boring, with radiation to the thighs and back, is ascribable to congestion and increased intracapsular ovarian pressure.⁷ Throbbing pains may be related to associated varicosities in the broad and infundibulopelvic ligaments. There is a serious doubt of the validity of these relationships, and many gynecologists feel that the non neoplastic cyst is not responsible for the pelvic pain of which these patients may complain.⁸⁻¹⁴ Pelvic discomforts are common and apt to be present in the neurotic and hypersensitive patient. Reproduction of the complaint by bimanual pressure on the involved ovary may be of some diagnostic help, but is not conclusive.

When these cysts are prolapsed into the cul-de-sac, deep dyspareunia may be the complaint. This situation can be managed by pessary support or appropriate coital attitudes.

Menstrual Disorders.—The pattern of endometrial growth, and menstrual shedding of the endometrium are directly dependent on rhythmic and balanced production of estrogens and progesterone in the ovary. Histologic examination of the non neoplastic cyst wall suggests that in

most instances it does not produce steroid hormones in significant amount However, those cysts lined by healthy granulosa or theca cells, which may be luteinized, may affect the endometrial pattern Since anovulation is the rule, the endometrium is in persistent proliferative phase, the shedding of which is apt to be focal, prolonged and bloody Hence mild degrees of menorrhagia might be encountered There may develop a "swiss-cheese" endometrial hyperplasia, a condition which depends on prolonged unrelieved estrinization, rather than an unusually high estrogen level ²² It is unlikely that a secreting follicle could attain the estrogen production characteristic of a normal corpus luteum The syndrome of follicular cystosis, endometrial hyperplasia and menorrhagia is not unusual in women, and is also encountered in monkeys and cows ¹⁰

Persistent and excessive prolan B production leads to preovulatory luteinization of the granulosa and theca interna, followed by oligomenorrhea or amenorrhea without endometrial hyperplasia ¹⁰ A post-ovulatory corpus luteum may persist in a cystic or an unaltered state, maintaining the endometrium in a secretory or deciduoid phase Usually the menses are delayed for only a short time, but either a persistent corpus luteum or a corpus luteum cyst may account for amenorrhea of abrupt onset, lasting months to years ³ Occasionally a prolonged amenorrhea, associated with intermittent secretion from the breasts, follows term pregnancy, owing to persistence of the pregnancy corpus luteum ¹⁷ The cause for amenorrhea in such cases is demonstrable by endometrial biopsy Amenorrhea is a more common manifestation in younger women, and excessive bleeding in the older group ²⁰

It is conceivable that a variety of other symptoms may have their origin in the ovarian cystosis Obesity, breast changes, sexual infantilism and a male type of hirsutes may be present ²⁵ In rare cases, distinct masculinization may occur ²⁹ Patients may have a variety of complaints, such as leukorrhea, frigidity, dysmenorrhea, urinary frequency and constipation, but one should be very hesitant to blame the cystosis These symptoms are common and nonspecific, and are almost certainly unrelated to the ovarian lesion

Non-neoplastic cysts are usually incidental findings, without any associated symptomatology None of the symptoms enumerated above are of specific nature, and they are common in women who have normal pelvic organs There is no way to establish a cause-effect relationship between cyst and symptom, except by a prolonged period of observation, and even this may be misleading Four hundred and forty-seven patients with small ovarian cysts seen in hospital practice had the gynecologic complaints listed in Table 1 Twenty-one and three-tenths per cent of these women were symptom-free After a period of observation the lack of

correlation between cyst and complaint became quite evident. In a group of 126 patients with cysts and pain, the cysts disappeared spontaneously in seventy four women, of whom fifty-five were relieved of pain. The cysts remained in fifty two women, but the pain ceased in forty-nine of these patients. Similarly, in a group of thirty-eight patients with cysts and dysfunctional bleeding, the cysts disappeared in twenty three women, of whom twenty-one returned to normal menstrual rhythm, and the cysts remained in fifteen women, but eleven of these had a spontaneous recovery of menstrual function, nonetheless. Cystosis disappeared

TABLE I*
SYMPTOMS IN 417 PATIENTS WITH SMALL SIMPLE CYSTS OF THE OVARY

| Symptom | Incidence | Percentage of Patients† |
|--|-----------|----------------------------|
| Abdominal pain | 183 | 43.2 |
| Altered menses | 110 | 26.9 |
| No symptoms | 63 | 21.3 |
| Miscellaneous symptoms (Dysmenorrhea, leukorrhea, sterility, dyspareunia, frequency, backache, constipation, headache, nausea, nervousness, weakness, etc.) | 153 | 34.2 |

* Modified from Miller and Willson.¹⁴

† Some patients had more than one symptom.

spontaneously in 59 per cent of the entire group, but whether it persisted or not, the patient was relieved of symptoms in 83 per cent of cases. In only thirty three patients an observation period seemed to establish a true cause-effect relationship, but surgical attempt to relieve symptoms was a failure in 10 per cent of these.¹⁴

Since cyst and symptom vary independently, a vigorous attack at the cyst in an effort to relieve symptoms is largely illogical and may involve an injustice to the patient. The role of the cyst, if any, is trivial and transient, and there is an excellent possibility that the symptoms will disappear without any treatment whatever. Treatment is more properly designed to offset the functional disorder. Vigorous treatment of a persistent cystosis is reasonable only when the associated gynecologic manifestation is chronic and disabling.

TREATMENT

Observation—Simple repeated pelvic examination is all that is necessary in the vast majority of cases. If the ovary continues to grow, without occasional reduction in size, the diagnosis of a true cystoma should recur to mind.

Improvement of Pelvic Mechanics—Correction of uterine retrodisplacement by postural exercises and vaginal pessary may improve pelvic circulation and relieve ovarian congestion and edema. Ovarian massage during bimanual pelvic examination is not widely employed, but may be of value in relieving passive congestion and as a nonspecific stimulus. Accidental or intention rupture of a thin-walled cyst may eliminate a mechanical and hormonal impediment to good ovarian function.¹⁸ Hemorrhage from a ruptured cyst wall is not likely, but the release of the cyst fluid may cause transient pelvic pain and peritonismus, of which the patient should be forewarned.

Control of Infection—Septic inflammation of the ovaries usually is followed by some permanent crippling of ovarian function. In the chronic stage antibiotic drugs are not of much value. Natural reparative processes may be accelerated by sexual rest and by induced pelvic hyperemia (hot douches, pelvic diathermy).

Hormone Therapy—The strong evidence for an endocrinopathic origin, and secondary secretion of steroid hormones by these cysts, suggests that appropriate hormone administration might correct the former and offset the latter. Because of the vague and variant endocrine background of the process, hormone therapy is largely empiric, and the results are not usually spectacular.

Treatment with gonadotropic extracts is probably worthless, and may accentuate the cystic change.²⁵ Whatever distortion of gonadotrope production may be present, it is apparently not correctible by currently available products.

Large doses of stilbestrol may reduce the incidence of ovarian cystosis. Karnaky has administered an average total dose of 155 mg to 869 patients awaiting pelvic laparotomy, and at operation the ovaries were said to be small and atrophic in appearance. Eighty-one women who had cystic enlargement of the ovaries were given 5 mg of stilbestrol for twenty to seventy days. In twelve cases the ovaries did not shrink. Of these, eight had dermoid cysts and four had parovarian cysts. This author recommends that women having cystic enlargement of the ovaries be given 5 mg of stilbestrol for thirty night doses. If the cysts do not disappear, laparotomy for a true cystoma is advocated.¹² He believes that the effect is a local ovarian phenomenon, and has employed injection of stilbestrol in oil through the fallopian tubes to bathe the ovarian surface. Massive inhibition of the pituitary may be the important factor. Subsequent changes in the ovaries are not described.

Progesterone therapy is quite rational in an attempt to engraft secretory changes on an estrinized endometrium. The breakdown products of

a secretory endometrium, and certain estrogen metabolites produced in the presence of progesterone may provide physiologic stimulation of the pituitary gland,²² and thus correct defective gonadotropin secretion. A short course consisting of several doses of 10 to 20 mg of progesterone may be given at monthly intervals, late in the menstrual cycle. This treatment may be valuable in relieving menorrhagia, if present.

Testosterone in doses of 10 to 25 mg several times weekly will inhibit excessive gonadotropic activity, and thus retard cyst development. At the same time it may control associated excessive uterine bleeding. In the amenorrhea due to a persistent corpus luteum, or a corpus luteum cyst, a single large dose (50 to 75 mg) of testosterone may offset the sustained estrogen and progesterone secretion, thereby permitting endometrial and pituitary escape and the return of cyclic menstruation.¹⁷ This can be a therapeutic test for the presence of persistent corpus luteum effect.

Endocrine treatment is not apt to effect a prompt reversal of the structural ovarian change. Hormones are valuable principally to regulate the endometrial growth pattern, and thereby control the menses. The hypothetical pituitary defect is best remedied by attention to its originating causes, which may be a deep-seated metabolic disturbance.²³

Surgery—Surgical interference with a process whose origins are only partly local, when the associated symptoms do not necessarily arise from the lesion itself, and when the lesion is apt to disappear without any treatment, is of very questionable value. Moreover, removal of the cysts may be followed by recurrence in the same or the opposite ovary. It is difficult to justify the social dislocation and loss of time involved, and to accept the hazards and possible damaging aftermaths of operation, which may include the perpetuation of a psychoneurosis.

Nevertheless, a great many women are subjected to surgery of expediency, after a hasty examination and a meretricious explanation. Women are prone to believe that their ovaries are readily inflamed, subject to decay and incipiently cancerous. The opportunistic surgeon who detects an ovarian enlargement is apt to advise operation as a prompt, lucrative and definitive answer to the problem. A wavering decision is fortified by his intention to remove the appendix, the presacral nerve and to shorten any loose ligaments present. While many patients enjoy a period of post operative relief, a large number have recurrence of the original complaints, and may be led to undergo additional operations for lysis of adhesions and the like.

Various surgical procedures have been employed (*a*) to remove local factors thought to have etiologic importance, (*b*) to remove the cysts in

order to control symptoms ascribed to their presence and (c) to correct changes of a self-perpetuating nature, permitting restoration of function in the remaining ovarian tissue.

Uterosuspension should rarely be the prime indication for laparotomy. While retrodisplacements, especially of the acquired type, may give rise to abdominal pain, backache, dyspareunia, and to secondary changes in the broad ligaments and adnexa, the possible benefits of a reposition operation must be demonstrated by preliminary pessary support. As incidental procedures during operation for more important conditions, utero-suspension and shortening of the ovarian ligaments are recommended.²⁸

Presacral Neurectomy—Presacral neurectomy is advised⁷ on the basis that disturbances in the vegetative centers can affect the ovaries via the sympathetic nervous system. However, ovarian innervation is independent of the presacral nerve.

Oophorectomy—Obviously, total resection of the ovary removes the lesion and its possible effects, and recurrence is of course impossible. The loss of one ovary is well tolerated, and the remaining ovary usually assumes the entire hormonal and ovular responsibility. In monkeys up to seven-eighths of the total ovarian tissue may be removed without subsequent menstrual change or loss of ovulatory function. With greater losses than this the remaining wedge of ovary develops follicular cystosis.¹⁰ Reduction of the ovarian mass beyond semicastration may lead to cystic change.³¹ Unilateral oophorectomy (usually the right side) is commonly performed, often in combination with appendectomy, after a vague preoperative diagnosis slandering each organ. The dictum that "an ovary is either good enough to let alone, or bad enough to come out" gains currency, because the partially bisected ovary is a possible site of recurrence or of future diagnostic confusion. While one ovary may be sacrificed with impunity, its absence is disastrous if the opposite ovary develops a cystoma later. Physiologic cysts that subsequently appear in the remaining ovary are not due to an increased biologic load, nor to a doubled weight of gonadotropic stimulus, but are usually a delayed appearance of the initial process. While the laparotomy has identified the original condition, there is no guarantee that the second ovarian enlargement is not a cystoma.

In hysteromyomectomies performed in the fifth decade or after, bilateral oophorectomy avoids such diagnostic dilemmas, which are more pressing in older women. Follicular cystosis is common after hysterectomies, but since blood supply from the ovarian arteries is so rich, it is unlikely that the loss of anastomotic supply from the uterine arteries could result in ischemic cystic degeneration of the ovaries. Even complete ligation of the blood supply to the rabbit ovary does not lead to cystic

changes.²² There is probably no embarrassment of circulation if the infundibulopelvic ligaments are not sutured to the cervical stump. It is more likely that follicular cystosis is related to the loss of a functioning endometrium.²³

Bilateral oophorectomy will certainly arrest the rare case of exsanguinating menorrhagia of the menarche, and teen age girls are sometimes mutilated in this manner (see Fig. 107). It should be remembered that follicular immaturity with anovulatory cystosis is common at puberty,



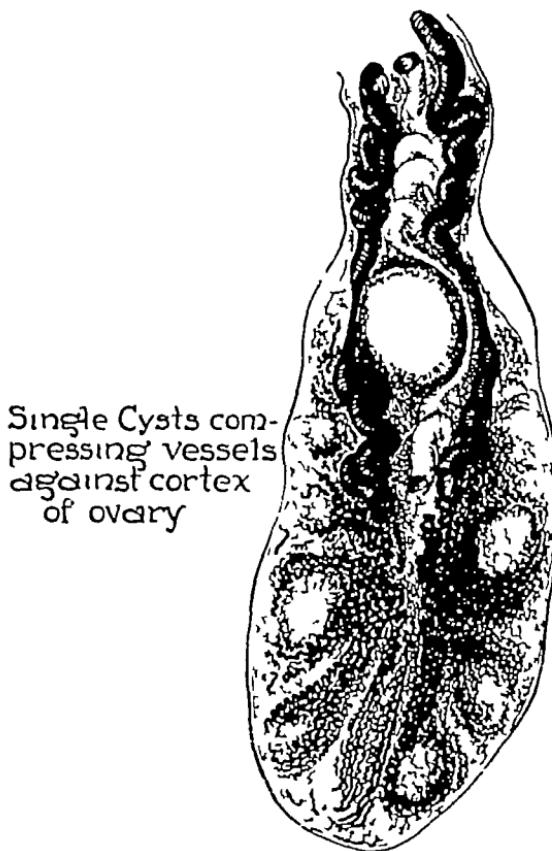
Fig. 107.—Multicystic ovaries removed from a girl aged 12.

and disappears with maturing pituitary-ovarian relationships. Hence palliation by any means, including multiple curettments, uterine packing and blood transfusions, will eventually be rewarded by the initiation of normal function. As a last resort, subcastration doses of radium (300 to 600 mg -hrs.) may be used.

At the menopause, cystosis with menometrorrhagia is readily controlled by a diagnostic curettage and a castration dose of radium (1200 to 1800 mg hrs.). Thereafter the ovarian enlargement recedes (if non neoplastic) and laparotomy is avoided.

Partial resection of the ovary is carried out to remove the local structural changes. Contralateral exsection of a wedge of cystic tissue, and puncture of other cysts, reduces pressure within the ovary, reduces edema, and permits better blood circulation. Since the remainder of the ovarian tunic

is as dense as theretofore and the remaining ovarian stroma retains its fibrosis, the advantage of the procedure is obscure. There may be damaging sequels, and the operation should not be lightly undertaken as a bounty incidental to other abdominal surgery. Simple puncture-decompression of the cysts is harmless. In chronic amenorrhea due to persistent corpus luteum cyst, enucleation of the lutein tissue may be the only possible cure.³



Single Cysts compressing vessels against cortex of ovary

Fig 198.—(Courtesy of Dr. Philip Jacobson¹¹)

Decapsulation of the Ovary—Operations on the normal-sized ovary have been advocated to correct similar local mechanical faults in the absence of cystic change. Jacobson states that cystic and sclerotic ovaries have the same clinical significance, the pathologic differences being merely variations of the same process. The common factor is an increased intrinsic ovarian pressure causing strangulation of the hilar vessels and nerves, usually following accidental follicle growth within the hilus (Fig 198). The elevated tension and the diminished blood supply seriously im-

pair cellular metabolism, and hence derange ovarian function. This situation is remedied by a partial decapsulization of the ovary.¹¹⁻¹⁵ The clinical indications for this operation are unduly vague.

Extrorotation of the Ovary—This operation (splitting the ovary and suturing the leaves outward) is performed to relieve pressure and to bypass the thick capsule which prevents follicle rupture. Baileya restored regular menses in thirteen of seventeen amenorrheic women treated by this method.²

Incision and partial resection of unenlarged ovaries has been recommended for chronic treatment refractory ovarian dysfunction. These operations can be performed by a vaginal approach through the cul de-sac,¹⁻²⁰ but inaccessible ovarian hemorrhage is a dangerous possibility. Operations on the apparently normal ovary approach the limit of surgical empiricism.

Surgical Restraint—Operation on the cystic ovary is an experiment justifiable only in terms of relief of symptoms. Unfavorable results do not inspire literary efforts, but occasional reports reveal surgical disappointment. In a series of ninety-three women operated on because of boring pains in the lower abdominal quadrants, forty seven continued to have pain corresponding to a resected or removed ovary, and twelve developed postoperative pain on the opposite side.²¹ In 165 operations on sclerocystic ovaries for persistent pain and irregular menses, eighty seven women were unrelieved, of whom forty five had a hysterectomy within three years.⁷ These two reviews show a 50 per cent success rate, which does not encourage surgery for functional disorders.

When the disturbance is pronounced, disabling and of long standing, and fails to respond to any other means of treatment, surgery may be the course of necessity. Robinson states that if a dysfunction repeats itself too frequently or forcibly, or persists long, the initial imperceptible structural alteration ultimately develops into definite and permanent organic entities. As long as the ovarian dysfunction still manifests a rhythmical character, broken and distorted as it may be, persist in opotherapeutic or nonsurgical treatment. As soon as the ovarian dysfunction becomes devoid of rhythmic significance (metrorrhagia or amenorrhea) the structural ovarian changes have become definite and fixed lesions and partial oophorectomy, is advised.²² In the occasional selected case of this type, operation is distinctly valuable. Stein and his associates²³⁻²⁷ have performed wedge resection in fifty three cases of polycystic ovaries (see Fig. 109) in women who suffered menstrual irregularities featuring amenorrhea, sterility, masculine type of hirsutism, retarded breast development, obesity and pelvic pain. There was a return of ovulatory function, regular menstruation, a growth of the

genital tract and breasts, and the cysts did not recur. Surgical success can follow only detailed, painstaking case study, and a policy of obstinate conservatism.



Fig 109.—Bilateral polycystic ovaries demonstrated by combined hysterosalpingography and pneumoperitoneum ("gynography") (Courtesy of Dr Irving F Stein)

SUMMARY

The intelligent management of the patient with a cystic enlargement of the ovaries involves a judicious consideration of its probable etiologic background, the nature of the ovarian dysfunction present, and the importance of associated symptoms to the patient concerned. The process is essentially benign and self-limited, and observation alone is more constructive than the many mutilating and unnecessary operations currently performed on these ovaries.

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THE ROLE OF CONTRACEPTION AND THERAPEUTIC STERILIZATION IN PREVENTIVE MEDICINE

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PREVENTIVE medicine is a term into which many meanings may be read, and I shall be rash enough to venture my own. I should like to divorce the term *preventive* from its restrictive and negative connotations and give it a positive one. I should like to persuade my readers to think of preventive medicine as the promotion of the health and happiness of individuals, rather than as an avoidance of something noxious. It is in this spirit that I will discuss the role of contraception and therapeutic sterilization in preventive medicine.

There is little argument today as to the ethical status and desirability of either contraceptive prescription or therapeutic sterilization where the individual patient is suffering from some progressive pathological entity that makes pregnancy a hazard to life itself. Such cases are, fortunately, few and far between, and yet there seems to be a great reluctance on the part of many, in the absence of organic disease, or what passes for it, to acknowledge the need in selected cases for the voluntary limitation of offspring. The willingness on the part of the physician to assume this responsibility often results in a degree of personal well being and effectiveness for the patient that would otherwise be sacrificed.

Family limitation is attempted universally, except where there is a total lack of responsibility. Therefore there is little need for the physician to feel that interest in the subject or skill in the detail of its prescription is a matter that does not concern him, or that it is undignified or unethical.

All married couples engage in sexual union at times with the hope that their indulgence will not result in a pregnancy. Their success in this respect is conditioned by their own self-control and intelligence, the information gleaned from friends and, in the last quarter of a century, from the more liberal of the medical profession. To be candid, up to the invention of the occlusive vaginal diaphragm about thirty years ago, the knowledge of the intelligent laity was equal to that of the medical profession in matters relating to family limitation. Consultation for the specific purpose of avoidance of conception was unusual since we had nothing new to offer. The advent of the occlusive diaphragm, however,

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produced a radical change, since instruction in its effective use requires the cooperation of a physician trained in this subdivision of gynecology The commendable zeal of those interested in the alteration of certain social evils to make this new discovery immediately available to the population as a whole resulted in the "Birth Control" movement, now called "Planned Parenthood" The medical profession, naturally conservative by temperament, and slow to realize the potentialities of the new discovery, were irritated by the fact that the chief agitation for its widespread employment came from lay sources Physicians were placed in the unhappy position of the rope in a well-contested tug-of-war, with each contestant sincerely convinced that only in the execution of his own program lay the best hope for a better world

I can best justify the optimism in my opening remarks by simply stating my own convictions in respect to the practice of family limitation It is my considered opinion that it is the prerogative of all married couples to have information that makes possible the exercise of their marital right with the reasonable confidence that an undesired pregnancy will not result In my own experience of twenty-five years' standing as a husband and a father of five children, I can think of no one factor which has added more to the joy and stability of our home than the fact that my wife and I were able to express ourselves in that particular respect with security and without revulsion I am convinced secondarily because of an ever growing group of grateful patients who have confirmed my own experience I invariably mention the subject to every private maternity patient under my care, and try to see that the same opportunity is extended to the ward patients for whom I am responsible I have yet to hear of one who was offended by the introduction of the topic

Naturally, patients must be individualized and my recommendations may vary from advising a patient to try to conceive as soon as possible, the best cure I know for the disappointment of an unfruitful pregnancy, to suggesting a postpartum tubal ligation for the purpose of permanent avoidance of conception In the broad sense, what I am advocating is routinely taking into consideration the reproductive aspect of each individual case as a definite and integral part of our normal obligation Prevention of conception represents only a single facet of the subject There are many equally important aspects

METHODS OF CONTRACEPTION

I think that anyone who has had a reasonable experience in contraceptive prescription cannot fail to be impressed by the fact that there is no one universally applicable method I will go even further and say that there may be indication for variation of method from time to time in the

same couple Obviously, the ideal method should be effective, extremely simple, and not cause too severe a rupture of the emotional continuity that should culminate in mutual orgasm This ideal method is yet to be found but fortunately there are available very fair approximations for many couples A brief review of methods with reference as to their particular suitability seems indicated

Complete Abstinence.—Contraception is defined in Dorland's Medical Dictionary as 'anything that prevents conception' The most effective contraceptive method, according to this definition, would be complete abstinence from coitus—a highly undesirable state of affairs in wedlock, even if the unremitting self-discipline and Spartan self-control required lay within the capacity of most individuals Viewed from this angle a devout churchman who limits his family by abstinence from sex relations, either complete or periodic, is practicing contraception

There are available, however, other and perhaps more acceptable methods That these methods are widely used is hardly a matter for argument

Coitus Interruptus.—The most widely practiced, I suppose, is 'coitus interruptus' Many couples have informed me that they prefer this method to the use of other more elaborate means, that it causes no emotional upset, that the self-denial involved is well within their capacity, and finally that they have a sense of security in its use

Douche—Next in popularity is the postcoital douche which may or may not be combined with coitus interruptus and other methods A large number of my patients inform me that they have practiced this simple preventive with confidence, comfort and success for years

Condom—The use of the condom, or male sheath, is widespread, particularly in urbanized segments of the population This method enjoys its greatest popularity where the female partner is too timid, too inhibited, or too feckless to employ a method that requires positive cooperation on her part. A large percentage of the population sincerely believe this method to be the most reliable in preventing conception. In my experience, many couples cling to it for this reason, although they are personally dissatisfied with many aspects of its use However, a very fair number of couples do not find it objectionable

Occlusive Diaphragm—The use of the occlusive diaphragm in combination with spermatoциdal jelly has proved itself to be a godsend to many couples for whom the use of the other methods just mentioned has proved either ineffective, or objectionable, or both Its greatest popularity is found where the female partner is relatively uninhibited about sex matters, and where a fair degree of personal privacy can be enjoyed

It is quite possible that in the near future the use of improved jellies

or suppositories alone may supplant the use of the diaphragm Such products are coming on the market, and once their clinical effectiveness is thoroughly demonstrated, I venture to prophesy that they will enjoy a wide popularity because of the simplicity of their use

Periodic Abstinence—Finally, I mention the method of periodic abstinence, it has a very definite place in our armamentarium Its effectiveness is obviously limited to those whose menstrual rhythm is regular A good deal of self-denial is involved in its practice, but that, in my opinion, brings with it very definite rewards I feel that all physicians would do well to become expert in giving simple and easily understood directions in its use to such patients whose beliefs require its employment I have many patients who have used the method with security and satisfaction

It is my experience that it is better not to advocate an alteration of method in family limitation where a couple is satisfied with the one that they are using Contraceptive prescription should not be divorced from an inquiry into the harmony, or lack of it, in the sex relations of any particular patient The physician can often be of great assistance in helping improve matters with a few timely suggestions as to sex technic and attitude towards sex matters in general Such discussions often give the physician the opportunity to encourage his patients to have more children rather than less I invariably warn against the misfortune of the "only child," and I emphasize the point that children much more than two years apart are apt to prove rather unsatisfactory companions for each other The natural tendency of most women is to bear and rear children, and encouragement from her doctor often helps to overcome hesitations engendered by *economic or other considerations*

Permanent Sterilization—Permanent sterilization by tubal ligation or vasectomy is a serious responsibility for any physician to assume, and yet there are many instances in which it honestly seems the best solution It has been demonstrated by a large series of cases that the operative hazard is minimal, both as to morbidity and mortality

Tubal Ligation—The technic of tubal ligation is pretty much a matter of choice for the individual operator Personally I prefer the Pomeroy method It is simple, atraumatic and therefore well suited to immediate postpartum practice It is the consensus that the optimum time for this procedure is from twenty-four to forty-eight hours following delivery, if it is to be done postpartum Of course the selection of the postpartum period is for the patient's convenience

The basic question remains When is the physician justified in assuming this responsibility? I doubt if any clear-cut rule can be applied I am sure that when any conscientious physician reaches the conclusion, after careful consideration, that the procedure is indicated for an individual

patient considered from the long range point of view, relatively few regrettable errors of judgment will be made.

Instances in which the indication is advanced organic disease are, fortunately, few and far between, even in ward practice. I think it may be helpful if I list two representative cases in which organic disease is not present and which in their own way present to me clear-cut indications. Let us first consider a multipara usually seen in her middle or late thirties. She is apt to be of the good mother type. She already has five, six, seven or eight living children. Although her health has not actually been seriously affected, the strain of bearing and caring for a large family is quite apparent. She herself is thoroughly aware that, if she is subjected to the strain of further pregnancies, her stamina will not suffice to do the job that she feels she must do. She has usually already tried various methods of prevention with lack of success. She is in short, pretty desperate. It has been my experience that when tubal ligation is performed in such a case you will have for all time a thoroughly grateful patient.

The second type is more difficult to portray in a few words but to me is equally clear-cut. The woman is usually in her middle or late twenties. She is and has been inadequate to cope with what is demanded of her since marriage, and particularly since the birth of her first baby. She may have two, three or even more children. Her life has been a series of frustrations, upsets and disappointments. Running through all this there has been a constant current of ill health, usually without an organic basis. She is usually a poor mother by reason of her oversensitivity, egocentricity and ill health. Another pregnancy would mean, as far as she is concerned, unmitigated, irrevocable, hopeless tragedy. She has usually failed with contraceptives, as with everything else. The results of tubal ligation in this type of case are not so dramatic and the tendency towards ill health is seldom entirely corrected, but an even worse state of psychosomatic invalidism will have been avoided for the mother, and the existing children will have a better chance in consequence.

Naturally one is often confronted with requests for tubal ligation to be performed postpartum when one is in honest doubt as to whether the patient's long range interests are being furthered by compliance. In such cases I have found it helpful to tell the patient that because I am not sure it will be in her best interests, I will not do it at that time. If, however, she and her husband want it done at the end of six months I will comply with their request. This postponement has the additional advantage that other operative gynecologic work can be performed coincidentally, and eliminates many patients who might be likely to repent their original decision.

Vasectomy—The fact that in a fairly wide obstetric experience I have never had occasion to refer a husband to a urologist for vasectomy is fair evidence that the indication is unusual. The chief value of the procedure lies in recommending it to young husbands who for purely selfish reasons request tubal ligation upon their wives. Needless to say, they do not choose to have vasectomy performed.

CONCLUSION

Consideration of the reproductive capacities of patients is a definite part of our professional obligation. Gynecologists and obstetricians, along with the general practitioners, can set the pattern for others to follow. I feel that when this practice becomes widespread the profession as a whole will have come closer to fulfilling its Hippocratic Oath.

THE Rh FACTOR IN OBSTETRICS AND GYNECOLOGY

LEANDRO M TOCANTINS, M.D *

OBSTETRICIANS and gynecologists had the Rh factor thrust into their everyday consciousness by the discovery in 1941¹ that this factor was related to the occurrence of posttransfusion hemolytic reactions and repeated abortions in pregnant women, and the appearance of "Erythroblastosis fetalis" in infants of Rh negative women.

A frenzied period followed, like that accompanying any discovery when the extent of its application is uncertain, technics involved are still imperfect and trained personnel is scarce. This phase is now over for the most part. It has left us with a body of facts that make it possible for the obstetrician and gynecologist to recognize and avoid committing errors unwittingly committed in the past, anticipate certain happenings and have a measure of success in preventing or correcting them.

It would serve no useful purpose to repeat at this time any of the now well known fundamental facts regarding the Rh factor. From the clinical point of view, the accumulated experience of the past two or three years has helped chiefly to reaffirm and perhaps to expand the concepts advanced earlier more than to bring out any essentially new ones. This discussion will therefore deal principally with what now seem to be fairly well established principles to guide the obstetrician and gynecologist in the recognition and management of disorders involving the Rh factor.

IMMUNIZATION AGAINST THE Rh FACTOR

A long trail of complications begins when an Rh negative woman becomes immunized to the factor. Many of the difficulties which follow would be surmounted if a way could be found to prevent the immunization. So far no effective means have been found of doing this. Once immunized, a woman remains so for the rest of her life. It becomes therefore essential that we acquaint ourselves with the known paths of immunization and refrain from practices which we know may cause it.

1. No woman, regardless of how young she is, should be transfused or receive any injections of blood without a determination of her Rh type. If she is Rh negative she should receive none but Rh negative blood. This is in addition to the standard group typing and cross matching. A trans-

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fusion (either intravenous or intramuscular) of Rh-positive blood during infancy or childhood may destroy an Rh-negative woman's chances of ever having a viable child. Fortunately, discovery of the Rh factor came at about the same time when the number of transfusions and blood banks grew to great proportions. Many more Rh-negative women who are now getting Rh-negative blood would have been transfused with Rh-positive blood, and some would have been immunized, were it not for our knowledge of the existence of this factor.

2 It has been brought out that immunization may result from the trauma involved in inducing an abortion. Levine² has calculated that about 0.07 cc. of blood in the course of the entire pregnancy may be all that is necessary to immunize the mother. Some persons are readily immunized even by these small amounts³ while others are not immunized at all even after injections of large amounts of Rh-positive blood. The reason for these differences is not clear and there is no way, short of actually exposing a person to the Rh antigen, of telling whether or not they belong to the group who become readily immunized. The action of the curettage required to terminate an incomplete abortion, and even an abortion itself without any mechanical interference, may make possible the absorption of fetal products by the injured endometrium and subsequent immunization of the mother. Levine⁴ drew attention to the higher incidence of abortion in women who give birth to infants with hemolytic disease than in other women. Rh-negative women abort because they have been immunized to the Rh factor previously and, conversely, may become immunized because of a previous abortion. One of the probable causes of hemolytic disease (abortion) may itself become one of the results of it. Chown⁶ judges that sensitization by abortion or transfusion is more lethal than that after one and perhaps more sensitizing pregnancies.

Moreover, there should be as little manipulation as possible and preferably no curettage of aborting Rh-negative women. Manual removal of the placenta with inevitable tearing of placental villi, or injury of the villi by prolonged labor, seems likewise to favor the entrance of fetal cells into the maternal circulation.

It is well known that the first-born child of an Rh-negative mother usually escapes hemolytic disease regardless of what may happen to the following children. However, about 10 per cent of Rh-negative women who deliver infants with hemolytic disease have never before delivered an infant.⁶ Yet, of a group of twenty-eight women with first-born infants with hemolytic disease, in only eight (28 per cent) was there no apparent reason (transfusions, abortions) for the immunization.⁷ A patient's statement that her first-born died because of an "Rh complication" must be interpreted with caution, in many instances further investigation,

including serological tests and inquiry into the circumstances of the delivery, will point to other causes.

At various times it has been suggested that other diseases of pregnancy are related to anti Rh immunization. Aside from abortions, there is no clear evidence that other complications of pregnancy such as eclamptic or pre-eclamptic toxemia or premature placental detachments bear any relationship to the Rh factor. Rh immunized women, furthermore, form only a small number of the large group of women with "habitual abortion". Indeed, the obstetric history of some mothers with latent diabetes resembles very much that of immunized Rh negative women.⁸ There is likewise scant evidence as yet for the statement that malformations are more common in infants born to immunized Rh negative mothers.

PREVENTION OR ATTENUATION OF INJURY TO THE INFANTS OF IMMUNIZED RH NEGATIVE WOMEN

It is clear therefore that prevention of immunization by avoidance of known immunizing practices remains at the present time our best weapon in combating hemolytic disease of the newborn. What then can be done for the already immunized mother with a history of abortions and still born babies?

Once a woman has been immunized to the Rh factor all subsequent Rh positive infants will have the disease, but all Rh negative children will be free from it. However, in a group of 102 children born to mothers who had previously had a child with hemolytic disease, only four were Rh negative while in a random sample of the population twenty nine would have been expected.⁹ This has been thought to be due to the fact that hemolytic disease is more prevalent in families in which the father is homozygous Rh positive. It seems that heterozygous Rh positive fathers are less likely to have infants with hemolytic disease.

The degree to which each Rh positive baby will be affected is difficult to predict. Generally speaking, when an infant has been severely affected by the disease, the subsequent infants will be likewise affected. If the child is born dead or dies soon after birth, the outlook for viable children in future pregnancies is almost hopeless. If the hemolytic disease in the first or second infant has been mild there is no way of telling whether subsequently born children will have a mild or a severe grade of the disease. Allowing a longer time to lapse between pregnancies does not seem to increase the probability of bearing normal children. An immunized Rh negative woman who remarries, and whose second husband is Rh positive, will go on having infants with hemolytic disease. If the new husband is heterozygous Rh positive, hope for infants without hemolytic disease is greater, since about one third of the siblings will be Rh nega-

tive Artificial insemination with semen from an Rh-negative donor has been tried, and results in the birth of normal Rh-negative infants^{10 11}

Efforts to attenuate the effects of maternal immunization on the fetus have taken several forms

1 Attempts to alter the permeability of the placental barrier and prevent the antibodies of immunized mothers from entering the fetal circulation and combining with the Rh-positive fetal red cells So far none of the procedures recommended has been successful

2 Prevention of further increase in the Rh antibodies of the immunized mother during the course of the pregnancy Methods advocated for this purpose have proved fruitless

3 Removal of the fetus from the mother at about the seventh month of gestation, thereby avoiding two months additional exposure to the maternal antibodies

It is becoming more and more apparent that the hazard of prematurity added to the almost inevitable acute hemolytic phase that follows delivery is fully as great or greater to the infant than the hazard of allowing the pregnancy to go to full term and dealing with an infant in perhaps better condition to withstand the hemolytic process At any rate, no fetus can be delivered sufficiently early to escape the process completely, since this begins early in pregnancy, whether or not antibodies are demonstrable in the mother's serum Though Diamond¹¹ reported good results from early cesarean section when a previous pregnancy had ended in hemolytic disease, Potter⁶ has not had a single instance of an infant who survived and was normal after an early delivery by cesarean section, when the mother had previously lost an infant from hemolytic disease

MANAGEMENT OF HEMOLYTIC DISEASE

An important point in the management is to be able to recognize hemolytic disease and to differentiate it from states presenting a similar clinical picture

Simple "physiologic jaundice" of the newborn appears between the third and fifth day, is usually mild and disappears by the tenth day In most babies a diminution in hemoglobin and red cells takes place in this interval but red cell levels of 3 million or therabouts are unusual, except in babies born prematurely *Premature infants* in general and infants who have received *severe birth trauma* with resulting large hemorrhages may be jaundiced for several days The spleen and liver are seldom enlarged in these babies and there is no evidence of immunization of the mother

Increase in the number of normoblasts and erythroblasts (normal for the first five days of life is 2000 per cu mm or under) may be seen after

asphyxia or prolonged labor without necessarily the presence of hemolytic disease. This is one of the reasons why the term 'hemolytic disease of the newborn' should be used in preference to the old term 'erythroblastosis fetalis'. Hemolysis is a constant component of the syndrome, but increase in erythroblasts may or may not be present. Moreover, an infant may have an increase in the number of erythroblasts without any evidence of hemolytic disease or Rh immunization. Jaundice of the *familial acholuric type* or that due to *congenital atresia of the bile ducts* should not be difficult to separate from that due to acute hemolytic disease.

Infants with *congenital syphilis* may present many of the findings associated with hemolytic disease (hypertrophy of the spleen and liver, anemia, erythroblastosis, edema and foci of extramedullary erythropoiesis). Evidence of syphilis in the mother and later on in the infant and absence of maternal immunization should help in the differentiation. Anemia due to *simple blood loss* during infancy may sometimes be baffling. In one of the infants we observed, the cause of a fairly severe anemia was obscure until it was disclosed that there had been bleeding from the umbilical cord intermittently for several days after birth. Infants born of mothers with overt or latent *diabetes* may behave clinically like those with hemolytic disease.¹² Serological (Rh and anti-Rh) tests may provide the only means of identification, since the obstetric history of the mothers resemble in many respects that of immunized Rh negative women.

There is no general agreement regarding the incidence of hemolytic disease of the newborn. Estimates run between one in twenty to one in fifty children born to Rh negative women. These varying estimates are due principally to different criteria for assessing the existence of the disease. Potter¹³ gives the incidence of the disease in *children of Rh negative women* as one in thirty seven births, while the fatal form is found once in every fifty-six births. The incidence of the disease among all births has been calculated as once in 252 births, with the fatal form being once in 392 births.¹⁴ A busy obstetrician would probably not encounter the disease in his practice more often than once every two years.

Preparations for the management of an infant with hemolytic disease make it necessary to be able to predict the disorder. Prediction of the occurrence and severity of hemolytic disease in future pregnancies of an Rh negative woman rests on the following points: (1) The history of past pregnancies; (2) Whether or not the husband is homozygous Rh positive; (3) The presence and intensity of Rh immunization in the mother and the trend of this immunization during pregnancy.

In general, the most constant and highest titers of anti-Rh agglutinins are found in pregnant women who are carrying an Rh positive fetus.

However, there may be no appreciable increase in antibodies throughout a pregnancy ending in the birth of an infant with a fatal type of hemolytic disease. This may be partly due to the fact that the fetus may absorb most of the agglutinins formed by the mother, so that there is no opportunity for a high concentration to be built up in the maternal blood. Conversely, the presence of an increase in the agglutinin titer during pregnancy is suggestive, but not conclusive, evidence of the presence of an Rh-positive fetus, a mother immunized by a previous pregnancy may respond by an increased degree of immunization to the mere presence of a fetus in the uterus. It is wise to be on guard against this form of anamnestic reaction,^{12a} for it has led in the past to the induction of labor or premature delivery of a fetus who is subsequently found to be Rh-negative.

According to Page, Hunt and Lucia,¹³ the proper interpretation of periodic estimations of the Rh antibody content of maternal blood may help in predicting the outcome of pregnancy in an Rh-negative woman. When Rh antibodies *first* appear less than ten weeks before term, there seems to be no cause for interference since most of the infants would probably be normal or near normal. If antibodies appear more than fifteen weeks before the time selected for induction of labor, interference is probably useless, since most of the babies would be severely affected or born dead. Termination of pregnancy, if at all advisable, should be done in only a small group of mothers in whose blood antibodies appear *for the first time* ten to sixteen weeks before the estimated date of confinement.

The first antibody determination should be done not later than the twenty-fourth week of pregnancy, if the serum is then free of antibodies but a significant amount appears later (that is, about the twenty-eighth week of pregnancy) consideration must be given to terminating the pregnancy in the next two weeks, especially if a subsequent antibody determination during this interval yields an even greater rise in the titer.¹³ In a patient who is already immunized by a previous pregnancy which ended in an infant with hemolytic disease, significant rises in antibody titer (above that before pregnancy) determined at the same intervals mentioned above, should be the guide as to whether or not pregnancy ought to be terminated. If this rise begins more than ten weeks before the expected date of delivery, there is probably little use in interfering, for there has been already too much damage to the fetus. If, in twice or more times immunized Rh-negative patients, the rise occurs less than ten weeks before confinement, interference may be risked but the prospects for getting a viable baby should not be held to be encouraging.

The immediate management of an infant with hemolytic disease de-

pends to a large extent on the intensity of the process. Except for the introduction of the substitution transfusion technic, the principles of management have remained about the same. In anticipation of the birth of an infant with hemolytic disease, preparation should be made to have Rh negative blood available. If there has been a history of previous infants with hemolytic disease and/or the mother is known to be immunized to the Rh factor, the cord at delivery should be clamped even before it stopped pulsating. This will reduce the amount of antibody-containing blood remaining in the fetus. It may be helpful, especially if the baby is already jaundiced or anemic, to give the infant 50 to 75 cc of Rh negative blood through the umbilical vein, as soon as the cord has been clamped. A suitable method of using the umbilical vein is as follows:¹⁴

1. The umbilical cord is cut at the tie and the vein located. If there is a thrombus in the vein it is removed.

2. A pliable plastic catheter (polythene tubing is suitable) just large enough to permit passage of a 19 gauge needle is introduced into the vein. Occasionally there is some resistance at the skin level but with a minimum of manipulation the catheter will pass easily through the umbilical vein and ductus venosus into the inferior vena cava.

3. When the catheter reaches the vena cava, blood appears at the outlet of the tube.

4. A 19 gauge needle is fitted snugly into the outlet of the catheter and attached to a three-way valve. The blood is then aspirated from a reservoir and injected into the infant. After the procedure is over, the catheter is removed and the cord is re-tied.

A similar arrangement may be used for a substitution transfusion when the degree of immunization and previous history of the mother are such as to cause one to anticipate a severe form of hemolytic disease. The technical difficulties surrounding substitution transfusion are so great that only those skilled in such procedures should attempt it. The transfusionist must be thoroughly familiar with all possible routes for injecting and extracting the blood (sagittal sinus, medium cephalic vein, radial artery).

The prevailing opinion still seems to be that the best use of transfusions is in the correction of anemia and in tiding the infants over until the hemolytic process spends itself. It does not seem that transfusions prevent the development of the disease in the infant, and it is even conceivable that they may, in an infant with a normal cell count, increase indirectly the destruction of the infant's own cells, leading to greater hepatic damage. Perhaps it is preferable to watch the infant closely, do blood counts twice daily and transfuse promptly if the cell count goes under 3,500,000, the spleen continues to enlarge, the baby is listless and the

jaundice is increasing. An effort should be made to keep the red cell count between 3 and 4 million.

A point that deserves emphasis is that the blood for transfusion should be freshly collected. This may be conveniently done by removing from a suitable Rh-negative donor 100 cc. of blood to which 12 cc. of sterile 4 per cent citrate solution has been added. Two syringes, of 50 cc. capacity each, are loaded with 6 cc. of the sterile citrate solution, the blood is collected directly into the solution mixed by tilting the syringe a few times, and placed in a sterile container. This does not mean that stored Rh-negative blood may not be used, the fact that sometimes this blood has been standing for several days, with the consequent increase in the fragility of the erythrocytes, makes it less desirable for use in a condition where it is of some importance to have as nearly intact red cells as possible. It is wise to be sure that the donor of the Rh-negative blood has himself not been immunized in the past against Rh-positive cells by one of the ways known to produce such immunization. For this reason, blood from Rh-negative *male* donors is preferable.

The difficulty of securing Rh-negative blood has encouraged some workers to use Rh-positive blood. These observers claim that equally good results may be obtained by using this type of blood and that, moreover, this speeds the elimination of anti-Rh-agglutinins from the infant's blood. It is now believed by the majority of workers that only Rh-negative blood should be used, Rh-negative red cells will not be agglutinated by antibodies in the baby's blood. The transfusion will then not only help to correct the anemia but also slow the intensity of the hemolytic process.

The amount of blood injected at one sitting should be no greater than 10 cc. per pound of body weight and the rate of injection should not exceed 5 cc. per minute. In skillful hands¹⁶ the blood may be infused by the drip method over a period of several hours. This makes it possible to introduce the necessary amount of blood (up to 20 cc. per pound of body weight) without repeatedly disturbing these often desperately sick and weakened children. The intravenous route is preferable, since the intraosseous route has not proved practical in most infants with hemolytic disease. More than the usual amount of resistance is offered by the bone marrow to the injection of blood.^{16 17} The bones of these children appear unusually dense on roentgen ray examination. Changes resembling those seen in syphilitic chondritis have been described, as well as other skeletal abnormalities.¹⁸

In most infants with hemolytic disease one or two transfusions suffice to tide them over the acute hemolytic phase which is most severe in the first forty-eight hours. An infant living past the third day has a good chance of recovering and after the fifth day is almost certain to survive.

In the days before vitamin K was available about one-third of the infants with hemolytic disease had a hemorrhagic tendency, intracranial hemorrhages being not uncommon.¹⁰ The use of vitamin K has corrected one of the defects complicating hemolytic disease (hypoprothrombinemia) and probably accounted for some of the improvement in the prognosis of the infant with hemolytic anemia even before 1941, when the proper use of transfusions and the mechanism of production of the hemolytic syndrome became better understood.

BREAST FEEDING OF BABIES WITH ACUTE HEMOLYTIC DISEASE

Because Rh antibodies are often present in the breast milk of mothers of babies with hemolytic disease, it has been thought unwise to have the mother nurse such babies. Cappell¹⁰ and others have noticed a slow recovery of the blood of such infants until they are weaned. Cathie¹¹ doubts that the antibodies ingested by the baby would escape being destroyed by the gastric juice or that they would be absorbed into the circulation. One hour's incubation of serum of high Rh antibody titer with the gastric contents of infants does not reduce the antibody content of the serum, but the feeding of adults and babies with a serum of high anti-Rh titer failed to produce anemia or to bring out any antibodies in the blood of normal adults and infants and of infants recently recovered from hemolytic disease. Cathie¹¹ believes that where weaning has appeared to overcome a slow recovery from anemia, the time of weaning has coincided with the time of spontaneous recovery. The same rapid onset of blood regeneration in apparently refractory cases has also been observed in infants breast fed from birth and in others which have only been artificially fed. The time when this regeneration is usually seen is in the second month of life.

It would seem that, though there appears to be no clear proof of a relationship between the presence of Rh antibodies in the milk and the continuation of hemolytic disease in the nursing infant, this possibility should nevertheless be kept in mind in the occasional patient whose recovery seems unduly delayed.

NOMENCLATURE

One of the difficulties of understanding the literature on this subject is the conflicting terminology used by various workers. At first the Rh factor was thought to be a single entity and a person was either Rh negative or Rh positive. Subsequently it was shown that there are at least six different Rh antigens. The original Rh nomenclature had to be enlarged to fit the needs of investigators and it gradually became un-

TABLE I
THE SEVERAL VARIETIES OF HUMAN RH ANTISERA AND THEIR REACTIONS WITH THE RH FACTORS OF HUMAN RED CELLS
AMERICAN AND EQUIVALENT ENGLISH DESIGNATIONS

| Human Rh Antisera | American Nomenclature | "Rh-Positive" Types of Red Cells | | | | "Rh-Negative" Types of Red Cells | | | |
|----------------------|-----------------------|----------------------------------|------------------------------------|------------------------------------|---|----------------------------------|-----|-----|-----|
| | | American Classification | | | | English Classification | | | |
| | | Rh ₀ | Rh ₁ (Rh ₀) | Rh ₂ (Rh [*]) | Rh ₃ Rh ₄ (Rh', Rh'') | cDe | CDe | CDE | cdE |
| Anti-Rh ₀ | Anti D | + | + | - | + | + | - | - | - |
| Anti Rh' | Anti C | - | - | + | + | + | - | + | + |
| Anti Rh'' | Anti E | - | - | + | + | + | - | + | + |
| | Anti C & D | + | + | + | + | + | - | - | + |
| | Anti D & E | + | + | - | + | - | - | + | + |
| Anti-Rh ₂ | Anti c | + | + | - | - | - | + | + | + |
| | Anti e | + | + | - | - | - | + | + | + |
| | Anti-d | - | - | - | - | - | + | + | + |

(Modified from Cappell, 1946, British Medical Journal 2 601 and Belding, H. W. and Ross, J. F., Medical Clinics of North America 31 1163, 1947)

wieldy English workers¹⁰ proposed using the letters C D E to designate the three principal Rh and Hr antigens as follows

| | | | | | | |
|-------------------------|-----|-----------------|-----|-----|-----------------|-----|
| American Classification | Rh' | Rh _o | Rh" | Hr' | Hr _o | Hr" |
| English Classification | C | D | E | c | d | e |

The Rh type of any given patient is made up not of any one single antigen indicated above but of a combination of any three of them. For example, an Rh positive patient whose type is classified as being Rh_o is now said to be type cDe. From the standpoint of analysis of inheritance of Rh types and the *written designation of types and corresponding antiseraums* the new classification is an improvement. When speaking, the necessity of using such expressions as small b, large C is somewhat awkward. In Table 1 are represented the various Rh groups and Rh antiseraums with their counterparts in the English classification. The table may be used as a reference to help interpret serological reports using the new classification. Clinically, the most important serum is the anti Rh_o serum, which agglutinates red cells of about 85 per cent of white human beings. It is the serum most generally used to separate Rh positive from Rh negative bloods and is referred to by the British as the anti D serum. Though for detailed work in special problems the adoption of the nomenclature mentioned above is necessary, for most clinical purposes the following information is sufficient:

1. Whether a person is Rh positive or Rh negative.
2. If Rh negative, whether anti Rh antibodies exist in the serum, and what their titer is, using saline or albumin as a diluent.
3. If the father is Rh positive, it is occasionally important to know whether he is homozygous or heterozygous. This may be done with the use of anti Hr serums and the results can be simply expressed as follows:

Rh+ Hr- (Rh positive homozygous)
 Rh+ Hr+ (Rh positive heterozygous)

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PRENATAL MANAGEMENT OF SYPHILIS WITH SPECIAL REFERENCE TO PENICILLIN THERAPY

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SINCE the publication of the original article by Lentz, Ingraham, Beerman and Stokes,¹ in 1944, and the review by Beerman and Ingraham² in 1945, considerable additional information, all favorable, has been collected on the treatment of the syphilitic pregnant woman to prevent congenital syphilis. Now published reports are available from at least six research groups Johns Hopkins³, Cleveland⁴, Bellevue Hospital, New York⁵, Chicago Intensive Treatment Center⁶, Gallinger Municipal Hospital, Washington, D.C.⁷, University of Pennsylvania.⁸ All of these reports are in accord as to the value of this treatment.

AVERAGE PERCENTAGE OF SATISFACTORY RESULTS

The publications from these five centers when added to our own experience at the Philadelphia General Hospital and the University of Pennsylvania total approximately 580 cases in whom the infant has been sufficiently followed to be certain of the outcome. Among these there has been failure in the sense that a living syphilitic infant has been born in only eleven instances or 2 per cent. This is unparalleled by any other type of treatment when a similar type of patient material has been used. The figure is the more noteworthy when it is considered that most of the women studied had primary, secondary or early latent syphilis in which circumstance expectancy of fetal infection would be greatest.

Unfortunately none of these recent studies has been controlled by comparison with results of untreated syphilitic pregnancies because no one desired to let syphilitic mothers go untreated and because medical care in all of the areas considered is so good that there are very few syphilitic pregnant women normally going without specific treatment. The excellence of the results must be determined by comparison with previous studies from former years.

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It is generally conceded that if a mother with symptomatic early syphilis remains untreated during her pregnancy the likelihood of her giving birth to a dead or diseased infant is better than 95 per cent. In the average prenatal clinic in which all stages of syphilis in pregnant women are cared for, syphilitic children will result about four times out of five in the untreated case. Arsenic and bismuth ideally applied under ordinary circumstances has given between 90 and 95 per cent satisfactory results with 5 to 7 per cent syphilitic infants. The syphilitic infant has most usually occurred when a woman with a recently acquired infection received substandard amounts of treatment close to term. Olansky and Beck's⁷ recent article compares the results of intensive arsenotherapy with penicillin therapy of the syphilitic pregnant woman.

It is evident, therefore, that a 2 per cent failure rate is better than has been obtained before. *There is no question that penicillin therapy of the syphilitic pregnant woman is the method of choice and that it should be routinely used in the treatment of all syphilitic pregnant women.*

THE ADVANTAGES AND METHODS OF ACTION OF PENICILLIN TREATMENT IN THE PREGNANT WOMAN

In addition to the usual advantages that it is *virtually reactionless*, that *treatment can be completed in a few days*, which means that the *whole treatment of the mother is usually given during the pregnancy*, considerations which in the past have always been important factors with patient control in the prevention of congenital syphilis, the most important advantage is that *penicillin permeates the placenta* from the mother to the fetus in what are apparently therapeutically effective amounts.

Woltz and Wiley⁹ at the University of Pennsylvania in a study of seven normal women have shown that penicillin given the mother readily passes through to the previable fetus between the ninth and twenty-fifth weeks in utero. Several reports show that penicillin easily goes through the placenta at or near term.

VALUE OF PENICILLIN IN LATE PREGNANCY

Clinic experience prior to the use of penicillin was that when the expectant mother had primary or secondary syphilis in the last month or two of her pregnancy the fetus was almost uniformly infected and born with active syphilis in spite of specific treatment. The most that could usually be hoped for was a living and treatable syphilitic infant.

Since the use of penicillin, such is no longer the case. In our own series 35 per cent of the mothers with symptomatic early syphilis were treated between the twenty-fourth and thirty-second week, 27 per cent after the

thirty second week, with almost uniformly satisfactory results. Several instances have occurred in which the treatment, delayed until the last week or two of pregnancy in a woman with secondary syphilis, has resulted in a "normal" infant at birth. We have seen instances in which the mother treated for early syphilis in the last few weeks of her pregnancy has given birth to a seropositive infant with roentgenographic evidence of healing bone lesions in which the process went on to complete healing and the blood serologic tests reached sustained negativity without additional postnatal therapy.

MOTHER USUALLY SEROPOSITIVE AT DELIVERY

The average period to reach seronegativity following penicillin therapy in the women which we have observed to become seronegative was 245 days (twenty five weeks). Since many of the women are not treated until the last half of the pregnancy the majority will still be seropositive at delivery. In our series treated with aqueous penicillin 72 per cent of the mothers had positive blood tests for syphilis at term, and in the group treated with penicillin in oil beeswax 85 per cent were still seropositive when delivered. *A negative maternal blood test at the time of delivery is accordingly not a requisite for obtaining a healthy nonsyphilitic infant.*

A single course of penicillin treatment any time during a pregnancy is usually all that is required to protect the fetus. After treatment the mother should have, once monthly until term, a physical inspection for the presence of syphilitic lesions and a quantitative titrated blood serologic test for syphilis.

Retreatment prior to delivery is to be considered if the mother fails to show a normal response. This would be evident in the early stages of the disease by recurrence of infectious lesions, by an initial decrease followed by an increase in titer of syphilis reagent in the blood serum (in its most marked form this response would result in a completely negative blood test followed by a reversal to positive), or by a sustained high titer. If the mother was originally treated during pregnancy for latent syphilis, which is the most common situation in pregnancy, a normal response is more difficult to estimate as most cases show no immediate decrease in the titer of the blood test. We have not retreated such cases, but have relied upon the initial standard amount of treatment which has been found to be effective in primary and secondary syphilis.

Where syphilitic infants have resulted it has usually been when the mother has had clinical or serologic relapse at or near term. The monthly follow-up through pregnancy with retreatment before delivery on the basis of the above criteria is accordingly necessary if results approaching perfection are to be obtained.

Mother Need Not Be Cured By Penicillin Treatment To Give Birth To A Nonsyphilitic Infant—Among the mothers whom we have treated there has been 5 per cent infectious relapse and 31 per cent serorelapse or seroresistance at the end of one year of post-treatment observation. Infectious relapse has occurred as early as four weeks following delivery in a mother who gave birth to a healthy infant. This situation is not much different than with previous methods of treatment in which there was usually no expectation of curing the mother during pregnancy even though a healthy infant was anticipated from judiciously applied treatment. Penicillin, in curing at least 70 per cent of these mothers *during* the pregnancy, has accomplished more than has been possible with any previous method of treatment.

MEDICAL FOLLOW-UP OF THE INFANT

Serologic Status of the Infant at Birth—Since the major portion of penicillin-treated mothers with syphilis are still seropositive at birth there is a transfer of syphilis reagin from mother to infant in many cases. The exact percentage of nonsyphilitic infants *seropositive* at birth will obviously depend upon the type of clinical material employed, the time in pregnancy the mother is treated, the height of the mother's reagin titer and exactly when the infant's blood is obtained for examination (e.g., whether cord blood is used or whether it is taken at varying times after birth in the nursery). In our group *40 per cent of the nonsyphilitic infants were seropositive* at birth and *100 per cent of our syphilitic infants were seropositive*. This means that only *73 per cent of our seropositive infants had syphilis* and points to the fact, as with other method of prenatal treatment, that a positive blood test on the infant at birth cannot be considered diagnostic of syphilis. The average duration to sustained seronegativity in our nonsyphilitic infants was between forty-five and fifty days.

Diagnosis of Infantile Congenital Syphilis—The following diagnostic criteria may be used in establishing the presence of infantile congenital syphilis in addition to positive darkfield examination of open skin lesions:

- 1 At birth, a confirmed titer of syphilis reagin in the infant higher than that in the mother (this is a very unusual circumstance)
- 2 A high sustained or increasing titer in the infant during the first month of life. In the nonsyphilitic infant an initially high titer will drop appreciably during the first three or four weeks of life. If no such drop occurs the infant is forming a syphilis reagin and should be treated.

- 3 A confirmed strongly positive serologic test after the age of three months (or earlier if the initial tests have been negative)
- 4 Unequivocal roentgenographic signs of osteochondritis and/or periostitis in the first three months. This sign reaches its maximum diagnostic value at about six weeks.

An infant who has been followed for six months without developing any of the above evidences of syphilis will not show subsequent diagnostic signs of infantile congenital syphilis. This statement can apparently be made without reservation.

Treatment has been withheld uniformly in our studies until a diagnosis of congenital syphilis was possible, based upon the above criteria. Treatment was commenced immediately when the diagnosis was established. In each instance the syphilitic infant has responded well to therapy with penicillin and has apparently been cured of his disease.

What the Ideal Follow up of the Infant Should Consist of — 1. The infant should have in the neonatal period (while in the nursery) a complete appraisal for syphilis including a blood serologic test and if this is positive a roentgenogram of the long bones.

2. The *seropositive* infant should have the blood test repeated at least two week intervals to determine the trend of the syphilis reagent content by quantitative titered tests. He should have the roentgenogram repeated at the age of 4 to 6 weeks. If the initial positive test becomes negative in a few days or a few weeks, he should nonetheless be examined at the age of 3 months and 6 months to be certain the blood test does not reverse to positive.

3. The *seronegative* infant of a syphilitic mother should have a blood test at 1 month, 2 months, 3 months and 6 months.

RESULTS OF VARIOUS TYPES OF TREATMENT OF THE PREGNANT WOMAN TO PREVENT CONGENITAL SYPHILIS

The following statements are based upon the published reports and a comparison of these results with the studies performed at the Philadelphia General Hospital and University of Pennsylvania.

Aqueous penicillin alone in amounts of less than 1.2 million units total dose over the seven and one-half day period or of 1.2 million units over a four day period has received a very limited trial and was soon abandoned because it was shown to be ineffective in curing maternal syphilis. In the few cases available for analysis 79 per cent living normal infants have resulted and 16 per cent living syphilitic infants (see Table 1). Of considerable interest, however, is the *small amount of penicillin which may protect the fetus irrespective of cure of the mother*. The most exaggerated examples

TABLE I
 RESULTS OF VARIOUS TYPES OF PENICILLIN TREATMENT OF THE PREGNANT WOMAN TO PREVENT CONGENITAL SYPHILIS FROM
 THE PUBLISHED REPORTS^{3-6, 8-10}

| Penicillin, Total Dose, Oxford Units (Millions) | Vehicle | Duration of Treatment (Days) | Metal Chemo- therapy Added | Outcome of Pregnancy | | | | Normal Infants No. | Per Cent | | |
|--|-----------|---------------------------------------|-------------------------------------|-------------------------------|----------|------------------|-----------------|--------------------------|-------------|--|--|
| | | | | Number Patients Treated | Abortion | Miscar- riage | Still- birth | | | | |
| | | | | | | | | | | | |
| 1.2 or less | 1 aqueous | 7 or less | no | 10 | 0 | 0 | 0 | 1 | 15 | | |
| 1.2 | 2 aqueous | 7 or more | no | 76 | 4 | 1 | 0 | 1 | 79 | | |
| 2.4 | 3 aqueous | 7 or more | no | 332 | 0 | 6 | 8 | 4 | 89 | | |
| 1.2 or less | 4 aqueous | 7 or more | yes | 91 | 1 | 1 | 3 | 1 | 67 | | |
| 4.8 | 5 oil war | 7 to 9 | no | 62 | 0 | 0 | 5 | 3 | 81 | | |

of this are in some of the cases in the series of Cole and his co-workers⁴ in which 1000 to 5000 units of penicillin given every three hours for sixty doses (totalling 60,000 to 300,000 units over a period of seven and one-half days) to women with symptomatic early syphilis were sufficient to protect some fetuses. In this respect penicillin therapy is similar to arsenic and bismuth treatment in that small amounts, insufficient to cure the mother, given in the latter months of pregnancy are nonetheless effective in preventing infection of the fetus. These observations emphasize the fact that recently acquired syphilis or syphilis in the incubation period such as is found in the fetus is much more amenable to small amounts of treatment than is a firmly established infection.

Aqueous penicillin alone in amounts of 1.2 million units or over in a period of seven to nine days has resulted in 4 per cent living syphilitic infants and 89 per cent normal infants.

When aqueous penicillin dosage is raised to 2.4 million units or more given over a period of seven or more days, the results in protecting the fetus approximate perfection. Less than 1 per cent living syphilitic infants have resulted (two infants among 332 pregnancies) and 98 per cent normal living infants. In this group both the syphilitic infants occurred at the Philadelphia General Hospital where likewise the largest group of cases were treated. Since this represents ideal treatment insofar as present studies go, the various investigations contributing to these results are summarized in Table 2.

A small group of cases has been treated with 1.2 million units or less of aqueous penicillin combined with small amounts of arsenic and bismuth. The results here are about comparable to those obtained with larger doses of penicillin alone. One per cent living syphilitic infants have resulted, with 91 per cent living normal infants.

Penicillin in oil and beeswax, 4.8 million units in seven to nine days, in one small group of cases¹⁰ has given results somewhat inferior to the best that have been obtained with aqueous penicillin, but still better than with other types of ambulatory treatment. Three per cent living syphilitic infants have resulted and 84 per cent normal living infants. The standard course consists of 600,000 oxford units given once daily at 4 P.M. intramuscularly for eight days. Particularly to be noted in this group is the number of stillbirths and neonatal deaths. These have usually occurred when the mother with symptomatic early syphilis reported late in pregnancy. They bring up the question as to whether the preparations of penicillin in oil and beeswax available during this study, when given once daily, were capable of producing for the entire twenty-four hours a sufficiently high blood level to satisfactorily treat the already infected fetus.

TABLE 2
TREATMENT OF SYPHILIS AND PREGNANCY AQUEOUS PENICILLIN ALONE 24 MILLION OR MORE UNITS IN SEVEN OR MORE DAYS

| Reported by | Number Mothers Treated | Outcome of Pregnancy | | | | | Normal Infant |
|--|------------------------|----------------------|-------------|------------|----------------|--------------------------|---------------|
| | | Abortion | Miscarriage | Stillbirth | Neonatal Death | Living Syphilitic Infant | |
| Goodwin and Moore ³ (1916) | 14 | 0 | 0 | 0 | 0 | 0 | 14 |
| Cole et al ⁴ (1940) | 11 | 0 | 0 | 2 | 0 | 0 | 9 |
| Speiser et al ⁵ (1947) | 45 | 0 | 1 | 1 | 2 | 0 | 41 |
| Aron, Barton and Bauer ⁶ (1947) | 81 | 0 | 0 | 1 | 0 | 0 | 80 |
| Olinsky and Beck ⁷ (1947) | 18 | 0 | 1 | 1 | 0 | 0 | 16 |
| U of Pennsylvania (1947) | 77 | 0 | 3 | 1 | 1 | 0 | 72 |
| Philadelphia Gen Hosp (1947) | 86 | 0 | 1 | 2 | 3* | 2 | 78 |
| Total | 332 | 0 | 6 | 8 | 6 | 2 | 310 |
| Per cent total | — | — | 2 | 2 | 1 | 1 | 93 |

* From infant diarrhea during epidemic in nursery

It has already been pointed out that one of the great advantages of penicillin given in proper dosage is treatment of the infected fetus in utero.

SUMMARY OF PRINCIPLES OF PENICILLIN TREATMENT OF THE PREGNANT WOMAN BASED UPON PRESENT KNOWLEDGE

1 Satisfactory dosage of penicillin to prevent congenital syphilis would seem to consist of a total of 2.4 million units or more given over a period of seven or more days. When the aqueous salt is employed the frequency of injection will usually require hospitalization. The treatment course should be the same as that generally employed for early syphilis. Forty thousand Oxford units every three hours for sixty injections will total 2.4 million units. Some prefer a somewhat larger total dose or more frequent administration (e.g., two hour instead of three hour interval). The protection of the fetus or its treatment in utero apparently does not require this but no harm can come of the larger dosage and it may produce a higher cure rate in the mother.

2 The results are so good with penicillin alone in this dosage, that there would seem to be little reason to add arsenic and/or bismuth to this regimen. It is possible to obtain comparable results with smaller doses of penicillin when arsenic and bismuth are used, but it is difficult to see where this is any great advantage since the number of injections is increased and new types of treatment, with their own hazards, are added.

3 There is not much choice between the effectiveness of aqueous penicillin and of penicillin in oil and beeswax with the possible exception of the case of early syphilis in late pregnancy when the fetus is most likely to be already infected. Under such circumstances it is essential to obtain a sufficiently high sustained level of penicillin in the mother to be certain that the fetus is treated in utero. Aqueous penicillin is effective for this purpose and should not be replaced by other preparations in this situation unless it can be certain that high sustained levels over the full twenty four hours are possible with the one injection a day techniques.

4 Full dosage of penicillin may be given from the start. Instances have occurred in which miscarriage or stillbirths have resulted during or shortly after the completion of penicillin treatment. Cases have also occurred in which a fetus undoubtedly living at the commencement of treatment has died during treatment. In such instances the fetus and the placenta have usually been so grossly diseased that it would not be expected that they could have been saved by any type of treatment. The failure has been in not getting the mother under treatment soon enough and has not resulted from the ineffectiveness or the faulty administration of penicillin.

THE QUESTION OF RETREATMENT IN SUBSEQUENT PREGNANCIES OF THE WOMAN WHO HAS HAD A STANDARD COURSE OF PENICILLIN FOR SYPHILIS PRIOR TO CONCEPTION

The final answer to this question is not possible, but some data is available and more is in the process of being collected.

Fundamentally the answer to this question depends upon faith in the ability of penicillin to cure syphilis. If the expectant mother has not been cured of her syphilis by the previous treatment, then there is no question that retreatment during pregnancy is essential.

It should be noted that in the pre-penicillin days, women "cured" of syphilis by arsenic and bismuth gave birth to normal infants without treatment during their pregnancy. Yet, for the average case with the average handling, retreatment in each pregnancy was considered desirable if we were to be absolutely certain of obtaining a healthy child. Penicillin treatment of the pregnant woman is more effective, safer and easier to give than the older type of prenatal treatment. There is all the more reason, therefore, to give it if in doubt. Under these circumstances it will be difficult to do away with this firmly established custom.

The material available for analysis comes from two sources. Speiser and his co-workers⁵ (June 1947) found one syphilitic infant among eighty-four mothers who had been treated for syphilis prior to conception but who had gone untreated during their pregnancy. In this single instance the mother was seronegative early in the pregnancy but underwent serologic relapse during the pregnancy which was not discovered until term. If it had been discovered the authors felt that birth of a syphilitic infant might have been prevented by retreatment. Thomas,¹¹ reporting for the same group in October 1947, stated that among this series of pregnancies, then 191 in number, two congenital syphilitic infants had been born with nineteen stillbirths or neonatal deaths and 170 normal infants. In an unpublished paper of the University of Pennsylvania group,¹² among fifty-nine adequately observed mothers untreated during the pregnancy fifty-three healthy infants, three abortions, one miscarriage, one stillbirth, one neonatal death and no living syphilitic infants resulted.

Combining the information from the New York and Philadelphia groups we find that among 250 pregnancies in which treatment was withheld two syphilitic infants (less than 1 per cent) have resulted, and 223 (88.9 per cent) normal infants.

CRITERIA FOR WITHHOLDING TREATMENT DURING PREGNANCY IN THE WOMAN PREVIOUSLY TREATED FOR SYPHILIS WITH PENICILLIN

If the woman has been treated for syphilis before she becomes pregnant and if it is decided to withhold treatment during the pregnancy, *it is*

obviously necessary that she be followed carefully until she comes to term to be certain that her disease is inactive. Such follow up would consist in a physical inspection and a quantitative titrated blood serologic test once monthly until delivery. If there is any evidence of activity of her disease, retreatment should be immediately instituted. It would seem that a rational standard for withholding treatment would be as follows:

1 *The woman was treated for symptomatic early syphilis* and had a normal clinical and serological response. By this we would consider that the lesions healed and did not recur, that the blood serologic test became negative and remained so, or that, using quantitative titrated tests, it was progressing to negativity, and the spinal fluid was negative.

2 *The woman was treated for latent syphilis*, showed no evidence of progression of her disease, maintained a negative spinal fluid and became seronegative or returned, quantitative titrated tests being performed in the same laboratory, a sustained constant titer of syphilis reagin, minor day-to-day fluctuation being considered unimportant.

3 *The woman was treated for symptomatic late syphilis* and sustained a normal response for the type of disease present.

The decision as to whether to retreat routinely the seropositive cases during each pregnancy is a difficult one and probably will continue to be so. In Speiser's and Thomas's patients 11 per cent of the women who gave birth to normal infants without retreatment during the pregnancy were seropositive. In the University of Pennsylvania group 27 per cent were seropositive. The most difficult decision to make is in the case of the woman treated initially for latent syphilis when a serologic response to complete negativity is apparently not necessarily to be expected. We have withheld treatment if the titer of syphilis reagin is dropping or is low and sustained. We have retreated if it is rising or is high and sustained.

The penicillin therapy of the syphilitic pregnant woman to prevent congenital infection gives as perfect an example of the triumph of preventive medical treatment as it is possible to obtain. When an infant with congenital syphilis results, the failure of treatment as such can almost never be blamed. Among the usual causes are lack of public education which results in inadequate prenatal supervision, and inattention to detail of medical follow up for syphilis which may result in the occurrence of an untreated active infection in late pregnancy. Present day treatment has reduced a tragedy of motherhood which not so many years ago gave rise to dead or severely diseased infants about nine times out of ten, to a possible failure rate of less than 2 per cent. There is little question that penicillin should be universally used in the prenatal management of syphilis.

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EVALUATION OF RADIOGRAPHIC PELVIMETRIC TECHNICS

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It was not long after the discovery of the roentgen ray and the advent of its use for medical diagnostic purposes in general that an attempt was made to use it as a means of study of the pregnant abdomen and pelvis. Not only was it used for the study of the position of the presenting part, the fetal lie, and the fetal pelvic relationships, but it soon became apparent that more exact internal measurement could be acquired than was possible by the usual external measurements of the mother. Thus was pelvimetry born and various methods of measurements have since been described. These methods are, for the most part, accurate enough for all practical purposes. They are also reasonably easy to use, particularly in the hands of the man who has devised the method. Some are more practical and easier to use than others, but regardless of their intricacies and varying practicability, their purpose has always been to correct for magnified distortion, so that the proper internal measurements could be obtained.

Any discussion of pelvimetry, however, must be preceded by a word of warning. In the first place, the clinician must be cognizant of the possible dangers incidental to x-ray exposure of the mother and fetus. The geneticists have in recent years warned of the production of mutations.¹ The fear of injury to mother and child did curtail the use of pelvimetric methods for some time. The facts of the matter are, however, that pelvimetry can be done without too much danger, provided that reasonable care is used. After accurate measurements of the x-ray dosage are made, we find that we do no more harm in the usual pelviographic examination than we do by the ordinary gastrointestinal examination, provided they are not repeated too often, and provided they are limited to the last trimester. With these facts known, there has been a revival of the use of the x-ray in obstetrics during the last two decades, and more particularly during the early thirties. At that time, Caldwell and Moloy² brought out their pelvic classification and emphasized the importance of the study of the pelvis and fetus at the time of labor.

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THE PHILOSOPHIC APPROACH

A second word of warning might be given to the clinician to avoid placing too much confidence in pelvic measurements alone. One should rather think in terms of a dynamic or philosophic approach to this particular problem. A quotation from the writings of the late Doctor DeLee³ will best explain what I mean.

"Since the x-ray cannot measure the strength of the pains or the moldability of the head, or the expansibility of the pelvic joints, or the mutation of the sacrum, or the rigidity of the soft parts, or the metabolism of the parturient, et al., you can see what a small role it plays in the routine conduct of the delivery," but, he says, to quote further, "I would not be without it."

This statement is worth serious thought. Fortunately, or unfortunately, babies have been born since Adam—countless numbers without the aid of roentgen diagnosis. The advent of the use of the roentgen ray did not make normal delivery possible, nor anything of the sort. Intelligent obstetrics and its practice did not begin with the advent of the real atomic era in 1895. Indeed man was born, he lived and he died without help of the roentgen rays at all before 1895. How then could one single modality be added to the armamentarium of the obstetrician which would overnight revolutionize and completely change the mode of attack in the management of the parturient? It is time, therefore, that those who thought such should be the case and have struck out to prove it, each in his own way, should realize this. Perhaps many of these men have never delivered a baby, nor have they been present to see the miraculous and unexpected happen in a particular case where the cards were apparently stacked against both the mother and child.

Many mechanically minded radiologists and clinicians have conceived various methods of getting an accurate measurement of both the fetus and the pelvis. Each procedure has usually been reported and, in many instances, considered to be quite accurate, particularly in the hands of the man devising it, and no one has any doubt that each one was proved to be physically and mathematically correct. The point is that in these efforts there was always a hopeful intent to produce a "rule of the thumb" procedure in which, if the measurements were accurate, a prediction as to the exact outcome of labor could then be given. The feeling was, in many instances, that by measuring carefully the volume capacity of the fetal head and pelvis, one could very easily say that this case would do badly, while this one would do all right. To see the fallacy of this, however, one has only to observe the occasional case of almost absolute disproportion in which the entire group of observers is surprised to see an

unusually easy labor result, or at least one which was fairly rapid in spite of the fact that the measurements predicted otherwise.

Again one will see two similar cases as far as measurements are concerned where the anthropological characters of one will allow a very easy labor and the other gives trouble. Moreover, the occasional case is found in which the measurements are unusually adequate and dystocia still occurs. In this case, the man who has made the films may give the obstetrician the false sense of security that everything is quite all right because the various measurements and bony landmarks were within the normal or larger than usual. The obstetrician apparently may not realize that difficulties can arise in the individual case in spite of adequate dimensions. He may forget that actual disproportion, or even borderline disproportion, is a cause for dystocia in only a small percentage of the total cases of difficult labor. Most clinics give this figure as from 8 to 10 per cent. It would seem, therefore, that the negative evidence is perhaps the most important—to rule out at least one cause for difficult labor.

Wherein then does the importance of the study of the pelvis at the time of labor come into play and what made Doctor DeLee say that he would not have done without it? I only cite him as one of the number of men who have said the same. It is simply this that the examination will give you such valuable evidence beyond the pure measurements that, at times, it is the most important single bit of laboratory data we have. In the first place, everyone recognizes now that the external measurements do not reflect accurately the internal measurements and therefore, if measurements are wanted, the x ray can give any dimension desired. But the ability to study the pelvic classification and fetal pelvic relationships far transcends the importance of the pure measurements and it is in this particular field where the x ray is of the most value. It is not so much a matter of the x ray saying that this case will have to be sectioned and this patient will not, but rather to call attention to variations of shape and size which may give trouble and put the obstetrician on his guard. Herein lies the reasonable or philosophic approach to the problem. If one encounters a small android type pelvis, one would be much more concerned than were one to find a normally shaped, relatively small pelvis, for an abnormal mechanism would be much more likely to prevail in the first than in the second. Aside from the occasional case of actual disproportion, in which one glance at the x ray films or even palpation of the mother's abdomen will betray the status, the other cases of disproportion are all borderline where one must, in every instance, take into consideration the general condition of the mother, the endocrine background, the age, and so forth—all of which will determine whether or not

the obstetrician should resort to cesarean section or permit a trial of labor for a short time. The true philosophic approach is the one which will allow the obstetrician to choose the important data that he sees and needs or to discard certain data entirely if they seem to conflict with the over-all clinical picture. The x-ray should complement the examination, not supplant it. If the complete data seem to be contradictory, one should repeat the examination and refrain from action until all concerned have been satisfied as to the proper approach.

It is because so much has been claimed for pelvimetric methods alone that the procedure has come into disrepute with so many obstetricians. Their feeling that a radiologist is trying to sell something is certainly true in some cases. However, if there is good cooperation between the radiologist and the clinician, this feeling will be dissipated. If the don'ts and the do's are given proper weight and a careful correlation of the clinical findings with the x-ray is made, all of the data will be put in its proper place and will receive the proper recognition. If we do not do this, then this important adjunct and complementary bit of laboratory work will certainly fall into disrepute.

The roentgen examination of the pregnant abdomen and pelvis may be the least important of our diagnostic measures. On the other hand, it can be of inestimable aid and we should not want to do without it. The warnings given in these remarks are to be observed by both clinician and radiologist. I think both of them are equally at fault in expecting too much from the x-ray findings at times.

TECHNIC OF PELVIMETRY

At the present time our routine technic includes a supine stereoscopic anteroposterior view of the pelvis. Lateral films are made for a silhouette of the pelvic structure as well as the abdominal soft parts. These are made in both the recumbent and erect positions. We sometimes take an additional 45 degree angle film for a view of the subpubic arch and for further study of the outlet. Golden and Ball⁴ have made use of the erect anteroposterior view, but we have not found this necessary.

For mensuration we employ the handy device described by Colcher and Sussman⁵ (Fig. 200), which gives us almost any measurement we may desire. Everything these authors have claimed for this apparatus and method of measurement has been correct as far as we can determine. The pelvimeter* used in this method is a modification of the Weitzner rule and consists of an opaque metal ruler with true centimeter scale perforations. This ruler is horizontal and swiveled on a projecting arm at-

* Manufactured by Picker X-ray Corporation

tached to a vertical stem, which is also calibrated in centimeters. The stem is attached to a horizontal base parallel to the perforated scale. Regardless of position, the scale is always parallel with the table top and the film. Thus, when x-rayed with the patient, the ruler will have the same distortion as the diameters on the same level and the ruler markings on the film become the centimeter scale and can be measured directly.

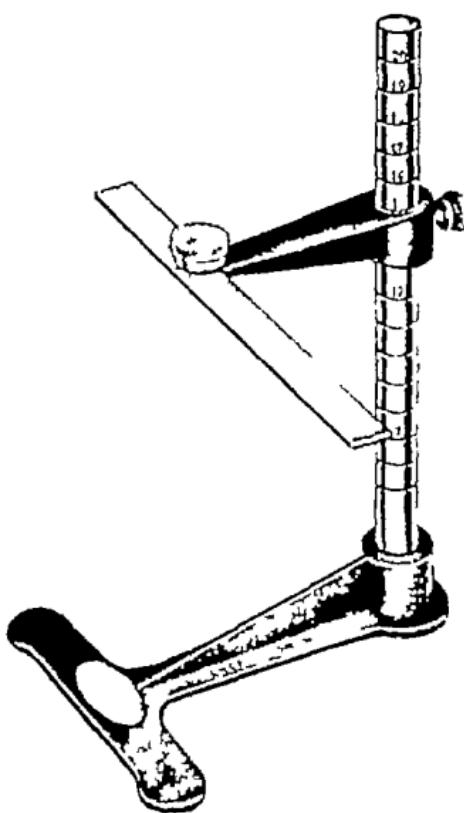


Fig. 200.—Colcher-Sussman pelvimeter. See text for description.

with a ruler. The position of the rule is checked in each case with stereoscopic anteroposterior films, to make certain it is in the correct plane (Figures 201 and 202).

Our film examination includes the following projections:

- 1 *Stereoscopic anteroposterior film of abdomen and pelvis*
- 2 *Erect lateral film for a study of pelvic architecture and fetopelvic relations at the inlet*

- 3 *Recumbent soft tissue lateral film* with special reference to the fetal skeleton and uterine soft parts
- 4 *An occasional anteroposterior of the sacrum and pubis angled 45 degrees towards the head* for a study of form and size of the pubic

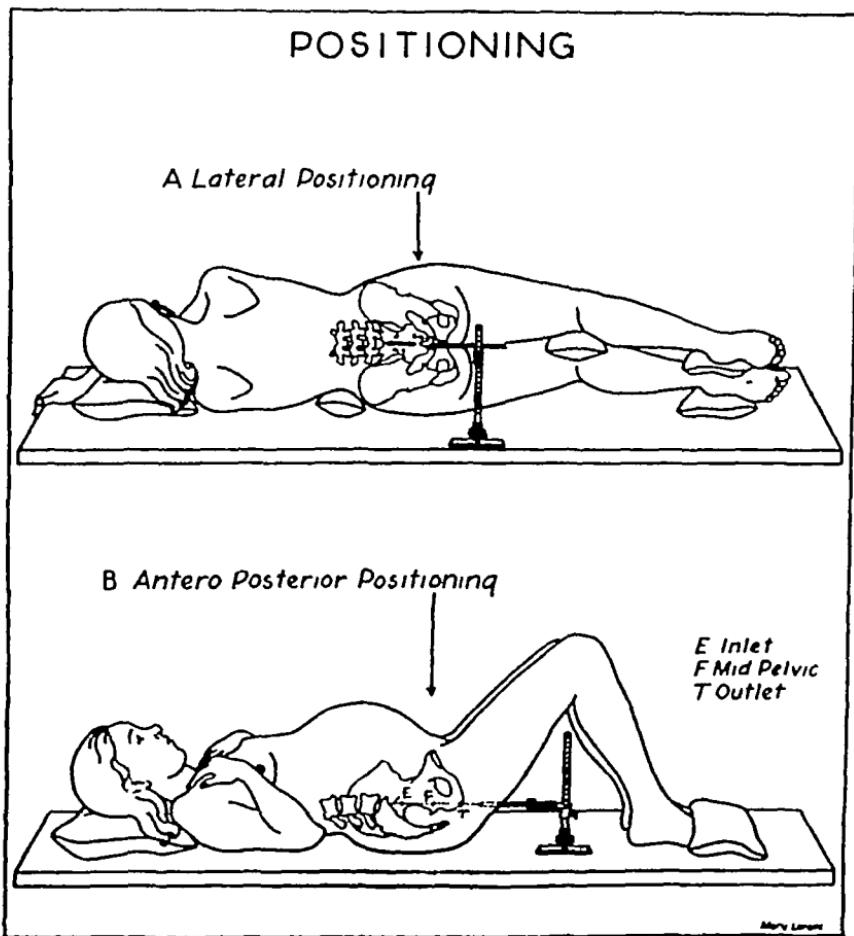


Fig 201.—Diagrams illustrating the position of the patient with the pelvimeter in place
(Courtesy of American Journal of Roentgenology.)

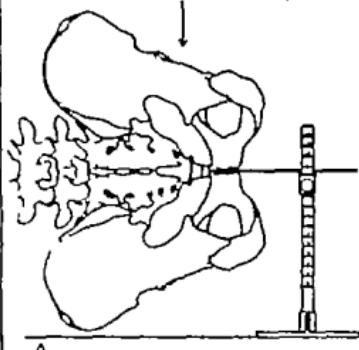
arch and architecture of the sacrum (An estimation of the pubic arch can be obtained from anteroposterior stereoscopy as well)

- 5 *In breech presentations* the ruler is placed at the midpoint of the fetal head by palpation before the recumbent lateral film is made
The technical factors are as follows

All films are taken at a 36 inch skin target distance with par-speed double intensifying screens using the Potter-Bucky diaphragm

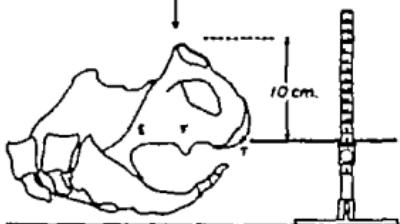
POSITIONING WITH RULER

Lateral Positioning



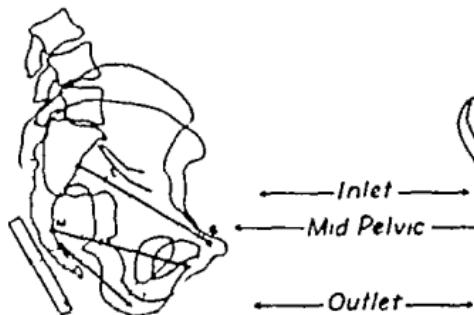
A

New Antero Posterior Positioning

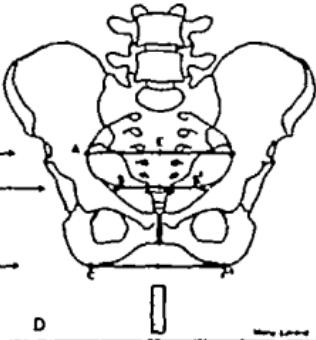


B

INTERSECTING DIAMETERS



C



D

Fig. 202.—Further diagrams illustrating pelvic planes measured. Note that in portion B the bi-ischial, bi-spinous and widest transverse are on the same plane as the pelvimeter rule when the patient is in this position. (Courtesy of American Journal of Roentgenology.)

The following range of factors is used for film exposures

Anteroposterior Stereoscopy of Abdomen and Pelvis

KV—65 to 78

Time— $5\frac{1}{2}$ to $10\frac{1}{2}$ seconds

MA—50

Frontal Lateral Film

KV—70 to 80

Time—7 to 14 seconds

MA—50

Recumbent Soft Tissue Lateral

KV—60 to 66

Time—3 to 6 seconds

MA—50

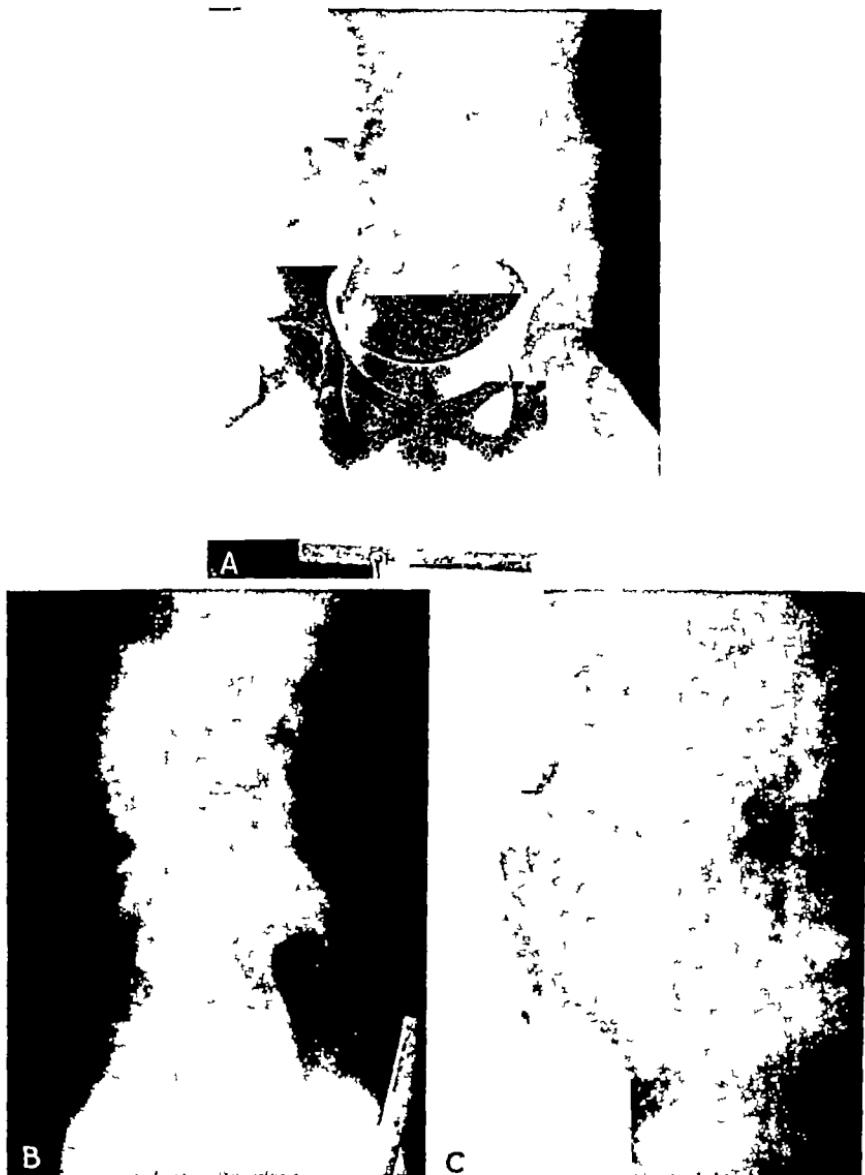


Fig 203.—Normal pelvis in a 22 year old white woman referred to the x-ray department for pelvimetry. This is a well formed pelvis with an anteroposterior diameter of 12 cm and a transverse diameter of 18 cm. The labor and delivery were normal. *A*, Anteroposterior film of the abdomen and pelvis—one of a stereoscopic pair. *B*, Erect lateral film. *C*, Recumbent soft tissue lateral film.



Fig. 204.—Large gynecoid pelvis in a 19 year old white woman in active labor sixteen hours. Despite the large pelvis this was a long hard labor probably due to resistant soft parts. *A*, Anteroposterior film of the abdomen and pelvis—one of a stereoscopic pair. *B*, Erect lateral film. *C*, Recumbent soft tissue lateral film.

APPLICATIONS OF THE METHOD

Thoms, in 1940, decried the fact that roentgen pelvimetry had been suggested as necessarily reserved for cases of disproportion, or of arrested labor. He points out that, in the light of the present knowledge concerning pelvic variations and anomalies, such an attitude is purely unscientific.



Fig. 205.—Twenty year old white woman gravida I, who was referred to the x ray department after twenty-four hours of labor with little progress. Films show the pelvis to conform to the flat type with the anteroposterior diameter of the inlet measuring 9.7 cm and the transverse diameter 19.0 cm. The head shows marked evidence of molding and in the erect position the head enters the pelvic inlet but is not engaged. The patient was delivered with midforceps after thirty-eight hours of labor. *A*, Anteroposterior film of the abdomen and pelvis—one of a stereoscopic pair. *B*, Erect lateral film. *C*, Recumbent soft tissue lateral film.

tific. We should be willing to use the roentgen ray almost as routinely as a blood count or urinalysis.

In 250 cases seen on the private service in two years time at Jefferson

Hospital, 25 per cent showed some peculiarity in the shape or size of the pelvis, but most of these were borderline. The examinations were made

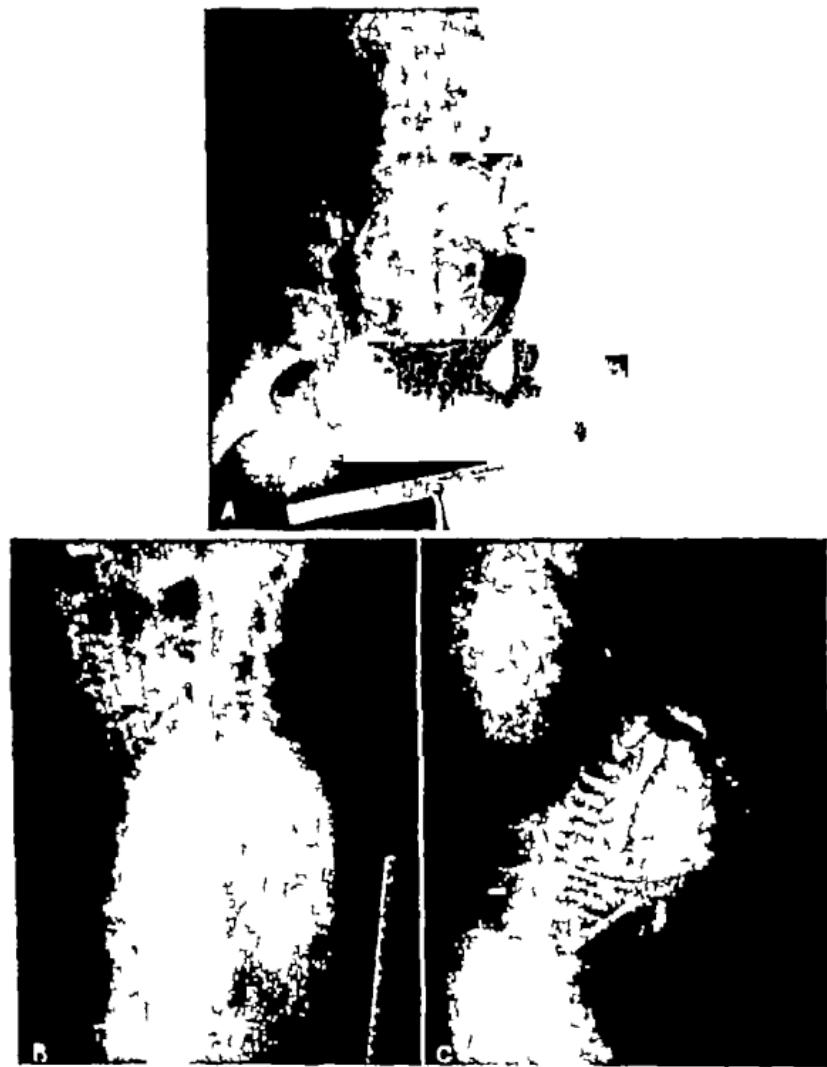


Fig. 206.—Anthropoid pelvis in a 20 year old white woman. The films show the head has adapted itself to the optimum position (posterior position). Labor and delivery were uneventful. *A*, Anteroposterior film of the abdomen—one of a stereoscopic pair. *B*, Erect lateral film. *C*, Recumbent soft tissue lateral film.

because the clinician suspected some disproportion based on the external measurements and conformation, or based on some suggestive past history. The most important data obtained was the negative evidence

given in the 75 per cent which showed no bony abnormality or disproportion. In none of the borderline cases did the measurements per se play a part in determining whether operative delivery should or should not be made. In those in which some slight disproportion existed, we were unable to predict whether labor would be difficult on this point alone. Often those cases that appeared most hazardous had the easiest delivery, since the efficiency of the forces of labor could not be predetermined. Only two showed absolute disproportion. Elective cesarean section was done



Fig 207.—Breech presentation. The films illustrate the use of the pelvimeter in estimating the diameter of the after-coming head. The ruler is placed at the midpoint of the head by palpation with the patient in the recumbent lateral position. *A*, Anteroposterior film of the abdomen and pelvis—one of a stereoscopic pair. *B*, Recumbent soft tissue lateral film.

in some of the borderline cases in which there was an endocrine background, or the age factor played a part. In these the clinician did not want to take a chance and the knowledge of the borderline measurements influenced his decision.

The midpelvic planes of measurements are perhaps the most important of all and should be given the greatest attention. The contracted midpelvic planes are more apt to cause difficult labor than any others. In their presence, the making of lateral films during labor to see how the head is progressing and adapting itself is all-important. I think it well to point out, however, that it is difficult to make a definite correlation of the so-called posterior sagittal measurement and the bi-ischial. It has been

suggested that, if the sum total of these two is under eleven, there may be trouble. This we have found to be unreliable in many cases, as so much depends on other factors such as head size, compensatory space in front, and force of uterine contractions. We have often seen this diameter relatively small and still have rather unexpected, fairly easy delivery. I do not believe a close correlation could be made.

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OBSERVATIONS ON THE USE OF VERATRUM VIRIDE IN THE TOXEMIAS OF PREGNANCY

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A PLAN for treatment of a clinical entity for which a definite etiological factor can be determined is in most cases not difficult to develop. For conditions such as eclampsia, however, we still are almost as confused as was Zinke in 1899 when in discussing a paper he stated — notwithstanding all the careful painstaking experiments that have been made in the past and present, we are today not one step further in our knowledge of this subject than we were ten, fifteen, aye, even fifty years ago. All we recognize is the plausibility that the cause of puerperal eclampsia is a toxicity of the blood, and that an imperfect or insufficient elimination of the effete elements within the circulation is probably to blame for the occurrence of the attack of convulsions. But the manner in which, or why, the enunctories cease to act properly or entirely, and how the poison or poisons act upon the systems, we do not know to this day.

That the mortality rate for this disease has gradually been decreased by several methods of treatment, some of which are diametrically opposed to each other, is further proof of the fact that the final answer has not been offered. The only satisfactory therapy for any condition is one which prevents or attacks directly the precipitating cause. For eclampsia this fundamental bit of information still has eluded the many investigators studying the condition.

Veratrum viride, a conglomerate mixture of alkaloids from the rhizomes of the green hellebore, was first used in the treatment of eclampsia almost a century ago. Since it slowed the pulse it was considered to be a substitute for phlebotomy which constituted a major part of any therapeutic regimen for convulsions in pregnancy. It is important to remember that at this time there was no method for determining blood pressure, proteinuria had just been discovered and almost nothing was known of the physiology of pregnancy, much less of the toxemias. We can, therefore, place little reliance on the early statistics regarding the treatment of eclampsia since, as is too frequently current even today, any patient who had convulsions during pregnancy was labeled as an eclamptic. The history of the use of veratrum viride and its physiological effects have been well summarized^{1, 2} and need not be repeated here.

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PHYSIOLOGY OF TOXEMIA OF PREGNANCY

The true toxemias of pregnancy, pre-eclampsia and eclampsia, are peculiar to pregnancy in the human being and have never been reproduced either in nonpregnant subjects or in experimental animals. It is for this reason that so little is known about the condition, patients with eclampsia must be treated rather than sacrificed to investigation as can be done in experimental physiology. In most instances there is a gradual progression through the initial to the severe stages of pre-eclampsia, followed by the appearance of convulsions and/or coma as the final picture. This increase in severity in the usual patient follows a definite pattern which can, by the alert attendant, be detected early in its course. The initial sign of developing pre-eclampsia is simply a rapid gain in weight which is the result of the characteristic but abnormal retention of fluid outside the vascular system. The reason for the reversal of fluid flow is at present not known, but when it is discovered the problem of toxemia of pregnancy may be solved. It undoubtedly is a result of pregnancy, usually the first, since eclampsia is most common in young primigravida and the ultimate cure is obtained only by delivery. That eclampsia ordinarily does not complicate subsequent periods of gestation is suggestive of the fact that not pregnancy in general, but a certain pregnancy is associated with the abnormality. Taylor, Warner and Welsh⁴ have noted fluid retention in gravid patients following the administration of the steroid hormones characteristic of pregnancy and a delay in postpartum diuresis when therapy is continued after delivery. This suggests that an imbalance either in hormone production or utilization may be responsible for the initial changes in pre-eclampsia. Fluid retention in almost every instance precedes the appearance of hypertension and proteinuria, the other two of the three cardinal signs of toxemia.

In the early case there is no other evidence of physiological alteration, renal function studies in mild pre-eclampsia reveal no evidence of reduced function or vasospasm in renal vessels, and no gross alteration in the retinal blood vessels is evident. Symptoms appear only after the condition is well advanced. It seems likely that the hypertension, which usually appears later than fluid retention, is a response to an unknown physiological alteration rather than the primary lesion. Progression in severity is characterized by increasing blood pressure, increasing proteinuria, increasing edema, oliguria, hemoconcentration and finally development of symptoms. In the advanced case evidence of vasospasm in the eye grounds becomes evident. The ultimate effect of these changes, convulsions or coma is probably the result of cerebral anoxemia which may be on the basis of cerebral edema, vasospasm or both. Improvement and re-

covery will only follow reversal of these pathologic changes. A plan of treatment which provides for dehydration of the tissues and hydration of the blood stream will usually result in control of convulsions, recovery from coma and resumption of renal function. If the abnormal changes cannot be reversed, death is likely to follow.

The control of blood pressure is of much less importance than the promotion of renal function and the control of convulsions. That reduction of blood pressure plays little or no part in recovery from eclampsia is evidenced by the fact that improvement following delivery (diuresis and control of convulsions) may occur despite the fact that the blood pressure remains at a level as high or higher than that before the uterus was emptied. While it is possible that a cerebral hemorrhage may occur in the eclamptic it is less common than with essential hypertension since the blood vessels are not structurally altered in this acute condition. It is likely that the hemorrhages which do occur are a result of rupture of a congenitally abnormal vessel. In any event a fall in blood pressure usually follows the administration of sedation in almost any regimen for the treatment of eclampsia.

PHYSIOLOGICAL EFFECTS OF VERATRUM VIRIDE IN TOXEMIA

There is no question but that the administration of Veratrum viride to a patient with severe pre-eclampsia or eclampsia is followed by a fall in blood pressure⁶ but it is questionable whether this is beneficial. Since the blood pressure rise in the toxemias is not the initial sign and since the outstanding physiological changes associated with progressive toxemia are decreased urinary output, increasing hemoconcentration and increasing extravascular fluid accumulation, it seems important that treatment be directed toward correcting these changes rather than simply lowering blood pressure. Veratrum viride fails to meet these requirements. The administration of the drug to a group of patients with severe pre-eclampsia was followed by a fall in blood pressure with a concomitant reduction in urinary output which averaged 95.7 per cent.⁸ That the oliguria and anuria are not initial effects of Veratrum viride which are corrected by continued administration of the drug is evidenced by the fact that in a group of toxemic patients treated over a period of hours with Veratrum viride alone there was noted no increase in urinary output as long as the blood pressure remained low. Only after the pressure approached its pre-treatment level did urine output increase.² Bourne⁶ in reporting a case of eclampsia, supposedly cured by the administration of veratrone, stated that the urine output was increased—however, when the volume of urine in each four hour period is compared with the systolic blood pressure it becomes evident that the lowest outputs are associated

with the lowest blood pressures which followed the injections of the drug (Table 1) The author has yet to see an increase in urine excretion following the administration of *Veratrum viride* Associated with the diminished volume of urine the urea clearance likewise drops⁶ Improvement in eclampsia and diuresis is noted only after there has occurred a reversal in the abnormal fluid exchange resulting in dehydration of the tissues and hydration of the blood stream Urine cannot be produced by the kidney from concentrated blood, but in most instances if hemodilution is accomplished fluid will be excreted That *Veratrum viride* plays no part in the important process of increasing plasma volume is evidenced by the fact that there is no alteration in hemoglobin or serum protein levels in toxemic patients to whom *Veratrum viride* alone has been given⁷

It is possible as stated by the older authors, that the drug will aid in controlling convulsions There is, however, no recent evaluation of the

TABLE 1
SISTOLIC BLOOD PRESSURE AND URINE OUTPUT

| Period (4 hours) | Urine Volume | Blood Pressure (Systolic) |
|---------------------|--------------|------------------------------|
| 1 | 90 | 96 |
| 2 | 150 | 160 |
| 3 | 60 | 125 |
| 4 | 60 | 120 |
| 5 | 120 | 135 |
| 6 | 100 | 148 |
| 7 | 90 | 136 |
| 8 | 80 | 110 |

effect of *Veratrum viride* alone on convulsions since all reports have included the use of sedatives which alone will accomplish the same result This aspect of the problem, however, deserves further study

RESULTS OF TREATMENT OF ECLAMPSIA

The reduction in mortality from eclampsia reported by the older authors following the introduction of *Veratrum viride* might be attributed wholly to the effects of the drug unless their regimens are compared with the treatment replaced For instance, Zinke reported a mortality of 13.3 per cent with *Veratrum viride*, as contrasted to his previous rate of 40 per cent⁸ His original management, however, was haphazard and the majority of patients were delivered immediately by manual or bag dilatations of the cervix or vaginal hysterotomy In the *Veratrum* series all were treated medically, labor was allowed to progress normally and delivery at the end of the first stage was carried out Early operative intervention without medical treatment in eclampsia always carries a

higher mortality rate than do the more intelligent forms of management. Thus it is likely that the discontinuation of accouchement *forcé* is in a large part responsible for the reduced mortality reported by the older proponents of the drug.

A compilation of statistics of the major reports in which Veratrum viride was the only drug administered or was included in the treatment of 486 patients reveals that the combined mortality rate is 9 per cent (Table 2). Torpin and Coppedge,²⁰ in reviewing a series of 350 cases of eclampsia, noted a mortality of 12.8 per cent. They state "During the time of the first half of this series the principal reliance for control of convulsions was placed upon Veratrum viride, and in the second half

TABLE 2
MORTALITY IN ECLAMPSIA TREATED WITH VERATRUM VIRIDE

| Author | Number of Cases | Deaths |
|----------------------------------|-----------------|------------|
| Fearn ¹ | 18 | 1 |
| Jewett ¹⁰ | 22 | 6 |
| Trimble ¹¹ | 26 | 3 |
| Ryder ¹² | 18 | 3 |
| Gillespie ¹³ | 18 | 4 |
| Zinke ¹⁴ | 50 | 4 |
| Haultaine ¹⁵ | 58 | 2 |
| Stevens ¹⁶ | 25 | 4 |
| Bryant ¹⁷ | 121 | 12 |
| Bryant and Fleming ¹⁷ | 120 | 2 |
| Greene ¹⁸ | 14 | 0 |
| Harkness ¹⁹ | 14 | 0 |
| Irving ² | 32 | 2 |
| Total | 486 | 43 |
| Mortality rate | | 9 per cent |

upon magnesium sulfate. Although for the first few years of its use magnesium sulfate was given in smaller doses and intramuscularly, the mortality of all cases in which it was used is slightly less than 9 per cent, a reduction of 35 per cent from the general mortality. Irving in comparing the mortality rates for Veratrum viride and magnesium sulfate regimens, concludes that the 7.8 per cent rate in patients treated with the latter preparation is higher than with the former. However, when a more complete tabulation of Veratrum series is included this is not evident. Other regimens of therapy not including Veratrum viride also will keep the death rate as low or lower.

MacCallum (1887)¹ 14 cases treated with chloral hydrate, chloroform, morphine and venesection—mortality 0

Solomons (1922)²² 204 cases treated with gastric lavage, magnesium sulfate, soda bicarbonate enemas and morphine—mortality 10 per cent

Gerrard and Newton (1932)²³ 60 cases treated by combined Rotunda and Stroganoff routine plus glucose and magnesium sulfate—mortality 5 per cent, 40 cases treated by the same method but without magnesium sulfate and glucose—mortality 10 per cent

Dieckmann (1941)²⁴ 75 cases treated with sedation, glucose and magnesium sulfate—mortality 6 per cent

It seems obvious from the reported results that little improvement can be expected when Veratrum viride is added to intelligent treatment programs. The lowest mortality rates are obtained when the drug is used in conjunction with a regimen of proven efficacy and it does not seem likely that it can be given credit for the result since in general the effects of its administration are opposite those desired in this condition.

THE PHYSIOLOGICAL TREATMENT OF ECLAMPSIA

There is no one preparation which will correct all the abnormal physiology which is responsible for the syndrome eclampsia, and any approach which is not directed toward reversing these changes will probably result in little reduction of mortality. Depression of blood pressure per se is of relatively little importance and in fact may be disastrous rather than beneficial since a fall in pressure and reduction in renal function go hand and hand. The most important steps in control of eclampsia therefore are in reversing the abnormal leakage of fluid into the tissues, promoting the output of urine and controlling convulsions. On the basis of our current knowledge the only part that Veratrum viride might conceivably play in such a program is in the control of convulsions, but since this also can be accomplished by other means it does not seem logical to add the undesirable factor of reduced urine output.

The convulsions are due to cerebral anoxemia which is a result of edema, vasospasm or a combination of the two. The anuria appears to be primarily the result of hemoconcentration since in most instances urine will be excreted if fluid is supplied to the kidney. Dehydration of the brain and extravascular tissues can be accomplished by reversing the flow of fluid back into the vessels and if this is accomplished the hemoconcentration is corrected and urine is excreted. This may be achieved rapidly by the administration of hypertonic glucose solutions which constitutes a major part of most successful regimens, even those in which the low mortality is attributed to Veratrum viride.

The following program for the treatment of eclampsia is neither new

nor original with the author but the principles outlined have been found to be safe and beneficial. In fact, the good results attributed both by Bryant and Irving to *Veratrum viride* were obtained with approximately this same regimen.

1 General Measures.—(a) The patient is kept in a darkened quiet room with constant attendance. In so far as is possible external stimuli are avoided.

(b) A constant supply of oxygen, by tent or mask, is provided.

(c) The urine is collected by inlying catheter and is measured and the amount recorded at thirty minute intervals.

(d) Blood pressure, respirations and pulse rate are recorded at thirty minute intervals.

(e) A mouth gag is at hand to insert between the teeth in the event of a convolution.

2 Sedation.—Oversedation to a point at which the patient is near death from the treatment is dangerous. There can be no "routine" orders for eclampsia; each patient must be treated as an individual problem, medications being ordered only as necessary for control of the disease.

(a) *Magnesium sulfate* in 50 per cent solution is injected deep into the gluteal muscles. Superficial injection may be followed by an extensive slough. This drug in addition to its central sedative action, depresses the nerve fibers peripherally at the myoneural junction and may also produce some vasodilatation. Thus it aids in the control of both convulsions and the elevated blood pressure in the eclamptic patient. The initial dosage is 10 cc and the medication may be repeated in dosages of 2 to 4 c after each convolution if necessary. *Magnesium intoxication* is not a problem, the first sign of overdosage is loss of knee jerks and even should this occur there is still a reasonably wide margin of safety.

(b) *Sodium luminal* has an action which is relatively slow to appear but prolonged and if given at the same time as the magnesium sulfate will reinforce the sedation. The initial dose of 0.32 gm may be repeated at eight to ten hour intervals as necessary.

(c) *Sodium amyital* may be given intravenously if the convulsions are occurring rapidly. The initial injection of 0.8 to 0.5 gm is given slowly and only enough is used for the immediate control, it usually is not necessary to repeat this drug.

(d) *Morphine sulfate* although it has certain theoretical disadvantages in eclampsia (increased intracranial pressure, decreased blood volume, decreased urine output and increased acidosis) is an important part of some regimens. The dosage is from 0.010 to 0.016 gm.

In most instances two of the above drugs are used initially, the usual

ones being magnesium sulfate and sodium luminal. Further sedation depends upon the response of the patient, but should never be carried to a point at which marked depression is present.

3 Reversal of Fluid Flow—One thousand cubic centimeters of 20 per cent glucose intravenously in forty to fifty minutes increase the osmotic pressure within the blood stream and extracts the fluid from the extra-vascular spaces thus diluting the blood and permitting the resumption of renal function. The brain is also dehydrated and usually the convulsions are controlled and coma relieved. There is no other method by which dehydration can be accomplished as quickly as with hypertonic glucose solutions, but in order to obtain the maximum effect the solution must be given rapidly. When administered over a period of hours it is metabolized and fails to increase intravascular osmotic pressure to a level at which efficient removal of fluid is accomplished. An equally important part of treatment with hypertonic glucose solution is that when it is administered the kidney, in an attempt to return the osmotic pressure to normal as rapidly as possible, responds by retaining the glucose and excreting large amounts of electrolytes. Since abnormal electrolyte retention is probably responsible for the accumulation of fluid (an effort to maintain a physiologic tissue solution), this is a distinct aid both in immediate and prolonged reversal of flow. The injection of glucose may be repeated at intervals of six to eight hours as indicated by the adequacy of urine output and general response of the patient.

4 Delivery—The primary treatment, unless the patient is in labor, is entirely medical since control of the toxemia is of utmost importance. In the majority of instances the delivery should be accomplished vaginally. If the cervix is "ripe" and there are no contraindications to vaginal delivery, labor may be induced by rupture of membranes after adequate medical treatment and control of disease. Cesarean section is permissible only if there is an obstetrical indication. The rare exception to this is in the patient who fails to respond to an adequate trial of medical treatment or the patient in whom the toxemia is controlled, and who cannot be delivered from below because of a long uneffaced cervix. In the first instance delivery is completed in an attempt to control eclampsia by emptying the uterus. The mortality is high and it is only a last resort effort when other measures have failed. In the latter case delivery is carried out during the period at which the patient is in good condition for surgery; eclampsia, in this instance, has been controlled but by no means cured.

Local or inhalation anesthesia, rather than spinal, should be used for delivery. Spinal anesthesia may be followed by vascular collapse with its added mortality.

5 Postdelivery Care.—Although the ultimate cure for eclampsia is delivery the danger is not over immediately since there is not an immediate reversal of the abnormal changes when the uterus is emptied. For at least twenty four hours, there still remains the possibility that the condition may recur or progress. As an aid in establishing the normal postpartum diuresis, hypertonic glucose solution is administered immediately after delivery and is repeated if necessary to stimulate the output of urine. Morphine sulfate 0.016 gm. or sodium amy tal 0.4 gm. is given in addition to sodium luminal in the immediate postpartum period and sedation is continued for at least twenty four hours depending on the condition of the patient. The same careful observations of urine output, blood pressure, pulse rate and temperature are continued.

SUMMARY

Intelligent programs directed toward correcting the abnormal physiological changes associated with eclampsia result in as low a mortality rate as those in which Veratrum viride is used. The effects produced by Veratrum viride are opposite those which are necessary for the control of eclampsia and at this time there seems to be no indication for its use.

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THE PRESENT STATUS OF CONTINUOUS CAUDAL AND SPINAL ANALGESIA IN OBSTETRICS

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CONTINUOUS CAUDAL ANALGESIA

DISCUSSION of the present status of continuous caudal analgesia in obstetrics necessitates a review of the history of its turbulent career since its introduction by Hingson and Edwards in January 1942. Anything that concerns the birth of a baby or the welfare of the expectant mother is a target for more than the usual amount of publicity. Anything that is publicized too much is frowned upon by the medical profession and is quietly condemned before it has had a fair trial. Unfortunately, continuous caudal analgesia was heralded by the lay press as a means of "absolutely painless childbirth" before this technic was even presented to the medical profession and, as in the introduction of twilight sleep, before its attendant dangers had been evaluated. Up to the present moment there is no such thing as "absolutely painless childbirth," and there is nothing on the horizon which would lead me to believe that this goal is soon to be reached. The obstetrician's aim has always been to give nothing in the form of drugs to the mother in labor that will have any effect on the baby. Except in the use of some form of regional block, all drugs given hypodermically, orally, by inhalation, rectally, or intravenously will have some effect on the unborn child. The effect varies, of course, with the stage of labor, the type of drug administered, and the dosage given.

Early Experience with Caudal Anesthesia—When continuous caudal analgesia was first advocated we had had a great deal of experience with twilight sleep, heavy barbiturate dosage, rectal ether, paraldehyde, and all forms of inhalation anesthesia. We had had a limited experience with local anesthesia, a commendable procedure in both vaginal and abdominal delivery, and following the development of fractional spinal by Lemmon, had reverted to the use of spinal anesthesia in cesarean section, having cast aside the single dose technic many years previously. Continuous caudal analgesia, therefore, seemed to be a valuable addition to our armamentarium. The thirty third woman to receive continuous caudal analgesia was a patient in the Philadelphia Lying-In Hospital, and the result in that instance was dramatically successful. However, the

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fact was immediately recognized that this was not a method to be used promiscuously or in surroundings other than in a well equipped maternity, administered by specially trained, competent individuals.

The United States Public Health Service assigned Hingson and Edwards to our Service at the Philadelphia Lying-In Hospital to evaluate this procedure. After careful study in the anatomical department of the Jefferson Medical College and discussion with our departments of neurology, pharmacology and physiology, a research program was established with the following aims in mind:

- 1 To determine, clinically and in the anatomical laboratory, the incidence of technical difficulties that might be expected from anomalies of the sacrum and from topographical obesity in the region of the sacral hiatus precluding the use of the method.
- 2 To determine the influence of this method of nerve block anesthesia upon the normal mechanism of labor.
- 3 To compare it with other methods of pain relief which we were already using in the vast majority of our cases.
- 4 To study the effects of the use of this method upon the fetal and maternal mortality and morbidity.
- 5 To follow our patients for a sufficient period of time to determine the incidence of complications associated directly with the method, and with the altered mechanism of labor produced by it.
- 6 To evaluate through the patients' expressions and reactions their own appraisal of this new technic in obstetrics.

In September 1942 Hingson and Edwards reported before the American Association of Obstetricians, Gynecologists and Abdominal Surgeons their experience in 560 labors. Their concluding paragraph stated "We emphasize that the method is one that should be studied in the large recognized obstetric clinics by men especially trained, before a final appraisal of its merits is given. It is not a procedure to be experimented with in an occasional case. There should be the utmost of cooperation between the physician anesthetist and the obstetrician in the handling of this procedure, which is vitally concerned with the principles of both specialists."

Contraindications—In 1943 I presented before the New York Obstetrical Society my observations in 927 labors under caudal analgesia and laid particular stress on the contraindications and the "don'ts" in the use of this method for the control of pain. I directed particular warning against its use by untrained individuals in poorly equipped hospitals, and emphasized certain definite *contraindications* such as:

- 1 Gross deformities of the spine, particularly of the sacrum.
- 2 Tumors which narrow the spinal canal.

- 3 Local infection around the sacral hiatus
- 4 Skin infections such as boils or carbuncles *anywhere* on the body
(A contraindication to be evaluated by the physician in charge)
- 5 History of sensitivity to the analgesic agent
- 6 Profound anemia, unless supplemented with oxygen inhalation
- 7 We have hesitated to use this technic in cases of placenta praevia because of the relaxation of the cervix and the possibility of bleeding This is particularly true if the patient has had any uterine contractions -
- 8 Floating head
- 9 Patients who have had known syphilis with probable central nervous system lesion
- 10 Obese persons
- 11 Dwarfs and midgets, because of low lying dura
- 12 Pilonidal cysts

In addition, we have avoided giving continuous caudal analgesia to patients in labor when the fetus is known to be dead or when a monstrosity has been diagnosed or is suspected We have also hesitated to give it when partial premature separation of the placenta is suspected

Premature Publicity on Method —By August 1945 we had used this technic in 2516 patients A careful analysis of our results was prepared by the statistical division of the United States Public Health Service and compared with 1024 consecutive patients delivered under some other method of pain relief We called upon this Bureau of the United States Public Health Service in order to obtain an unbiased evaluation of these studies, and through the use of the punch card system our results were compiled from our records by impartial individuals From these 2516 case histories approximately seventy five different observations were routinely recorded Before these studies were reported on September 1946 about 1000 additional patients in our clinic had received continuous caudal analgesia, but because of the great number of figures and charts involved, these case histories were not included A careful study showed, however, that they would not have altered our conclusions This report was presented at the September meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons in Hot Springs, Virginia, but, unfortunately, it was published only in the Transactions of this society Our failure to present our results to the entire medical profession by publication in one of the national journals was due to the fact that, although we had a verbal agreement with the United States Public Health Service that their statistical division would not use these statistics until we had an opportunity to give our results to the medical profession they published on November 29, 1946, in *Public Health Reports* (Vol 61,

No 48) a complete resume of our statistical data. The lay press seized this public report like hungry wolves, and caudal analgesia had a body blow dealt before the medical profession could be made aware of our results. Because of the lay publicity, the editor of the *Journal of Obstetrics and Gynecology* very justifiably refused to publish our paper. I am only mentioning this in an attempt to give the true story of the development of caudal analgesia, which must include of necessity the many obstacles encountered.

Results in 2516 Labors—Limited space does not permit an abstract of our results taken from the study of 2516 patients delivered with continuous caudal analgesia compared to a control group of 1024 patients delivered under some other form of analgesia, but I would like to list a few of the results without elaboration.

1 Ninety and four-tenths per cent of the mothers received complete relief from pain, 4.3 per cent received partial relief, and in 5.3 per cent there was failure to obtain relief.

2 Contrary to the overenthusiastic appraisal of the lay press and of misinformed persons in our own profession, we have never advised the institution of continuous caudal analgesia for the entire period of labor, particularly for the annoying discomforts of the early first stages. Our records indicate that the average duration of management of primiparous patients with this technic was 3.6 hours of the total of 11.6 hours of labor. The multiparous patient was managed with this technic for a period of 2.3 hours, three hours being the average for the whole caudal group.

3 The incidence of morbidity in the caudal group was 7.4 per cent and in the control group, 10.8 per cent.

4 The incidence of operative deliveries in the caudal group was 68.3 per cent and in the control group, 56.4 per cent. There is no question that a higher incidence of operative deliveries occurs when caudal analgesia is used, but low forceps and even rotation of posterior positions is more easily accomplished under caudal analgesia than under general anesthesia.

5 Forty-eight and five-tenths per cent of the mothers had a systolic blood pressure drop of 1 to 20 mm. of mercury, 39.7 per cent had a systolic blood pressure drop of more than 20 mm. of mercury. In practically none of these patients was a prophylactic vasopressor drug administered. Most of the patients who developed hypotension were among those studied very early in the series. It has been our experience that both the mother and the baby can be managed safely with a systolic pressure in the mother of 100 mm. of mercury. In hypotension below this level we recommend the prophylactic administration of a vasopressor drug. In addition, the complication can be easily combated by the simultaneous

administration of 100 per cent oxygen and, to provide an autotransfusion in the mother, by raising her lower extremities to right angles with the long body axis. This hypotension very frequently developed when the patient was moved from the lateral position to the dorsal supine position as in transferring the patient from the labor room to the delivery table immediately after the administration of a supplementary dosage. We recommend that those patients who require a supplementary dose of the drug preceding delivery be moved first to the delivery table and placed in lithotomy position in stirrups.

6 The average blood loss was 127 cc per patient, 16 per cent of the total number of patients lost 500 cc.

7 In the caudal group the third stage of labor lasted less than five minutes in 50 per cent of the cases and less than three minutes in 30 per cent of the cases. The corresponding figures for the control group were 34 per cent less than five minutes in 34 per cent and less than three minutes in 21 per cent.

8 In the caudal group 16.7 per cent of the mothers had one or more catheterizations as compared with 14.2 per cent in the control group. It has been our observation that if the bladder is allowed to become over-distended during labor, catheterization has almost always to be employed during the first twenty-four to forty-eight hours. This is particularly true if the patient is being managed by caudal analgesia, because the position of the patient on her side sometimes conceals the bladder distention.

9 In the caudal group 16.8 per cent of the mothers experienced severe after pains, in the control group, 22.4 per cent. It should be pointed out that all of the caudal patients received $\frac{1}{2}$ grain of morphine before leaving the delivery room one hour after delivery. This unquestionably diminishes the incidence of the complaint of pain in the early puerperium.

10 In the 2516 patients, four infections occurred at the site of injection, an incidence of 0.16 per cent. Two of these infections were extremely mild and superficial, and two developed a fairly severe cellulitis. Of the latter, one responded immediately to x-ray therapy and one had to be evacuated by surgical incision. These infections also occurred early in the series and with the refinement of technic we have had no infection since 1944.

11 In this entire series we did not find any late neuropathies in our follow-up study, 26 per cent of the multiparas were delivered under caudal analgesia for the second time. Immediate nerve complications occurred in two patients in the form of mild foot drop and both recovered completely. In both of these patients there was some question as to whether or not the caudal technic was actually the cause of the condition.

12 There were two maternal deaths which occurred suddenly forty-eight hours after delivery. The first one resulted in a case which was proved to be chronic bacterial endocarditis with positive cultures of *Streptococcus viridans* obtained at autopsy from the mitral valve. The cause of the death was given as an exacerbation of a mitral endocarditis. The second patient died two days after delivery, very suddenly. Autopsy diagnosis was syphilis, thrombophlebitis and intraventricular hemorrhage. This patient was an emergency case and was later found to have had a positive Wassermann reaction.

So much data was made available from this study that a separate report of results concerning the newborn was published in the *Journal of the American Medical Association* in the January 24, 1948 issue (136 (4) 221-229). Here again the results were dramatic. Of the babies delivered under continuous caudal analgesia, 3.6 per cent had delayed initial respirations beyond two minutes, as compared with 9.6 per cent in the control group.

Therapeutic nerve block in the treatment of vascular and renal emergencies with continuous caudal and continuous spinal analgesia and anesthesia has been discussed in a paper by Hingson, et al., in *The Southern Surgeon*, August 1947 (13 (8) 580-609).

Cesarean Section under Caudal Analgesia—During this time we also used the caudal technic in cesarean section in a total of 161 cases. In a report of 112 cases presented in the *American Journal of Obstetrics and Gynecology* our findings were summarized as follows: "Cesarean section under continuous caudal analgesia was performed in 112 cases with perfect results in 108. There were 4 failures attributed to inability to introduce the analgesic agent into the sacral canal. There were no maternal deaths, and no serious postoperative complications. There were 3 cases of morbidity, but these are not attributed to the use of the analgesia. One baby death occurred in a $5\frac{1}{2}$ months' gestation and the other 111 babies were discharged from the hospital in good condition. Due to an improvement in technique, the blood pressure drop in our recent cases was less than previously reported." The results in the remainder of this series of 161 cases were just as satisfactory. Since we were at that time becoming more interested in fractional spinal anesthesia in cesarean section as we found it so much easier and quicker to obtain a satisfactory level of anesthesia, we relegated the use of continuous caudal analgesia to two classes of cases: (a) those in which preliminary studies have indicated the possible need of cesarean section, in which case the same analgesia is continued for the operative procedure, if it is decided upon during the course of labor, (b) cases of severe pre-eclamptic toxemia in which treatment has failed to improve the patient's condition and termination of

the pregnancy is decided upon and is to be accomplished by the abdominal route in spite of the possibility of convulsive seizures. On two occasions I have had patients go into eclamptic convulsions with the abdomen open under local anesthesia, and I know of no more harrowing experience in surgery. In these patients, if the caudal analgesic is given slowly without any vasopressor drug, the blood pressure is sometimes reduced as much as 100 mm. of mercury, and I believe the possibility of ensuing convulsive seizures is minimized. Our experience with a number of these patients has been very satisfactory.

During the year 1947, and to date in 1948, we have continued the use of continuous caudal analgesia in our clinic. During 1947 approximately 48 per cent of my private patients were delivered with this method.

Conclusions.—What have we learned from six years of study and investigation of continuous caudal analgesia in obstetrics?

1. The same contraindications and 'don'ts' of this technic which we stressed in our early publications in 1942 and 1943 still hold good in 1948 and should be rigidly adhered to.

2. The greatest mistake was made early in the study, when caudal was administered too early in the labor. It is not a panacea for all of the pains of childbirth, and we had not observed the technic for any great period of time before we realized that the patient must be in active labor (ideally 4 to 5 cm. dilatation with good contractions five minutes apart). This was borne out by our unpublished report of over 2000 cases in which the average time of management under caudal analgesia was 3.6 hours of the total of 11.6 hours of labor. It is not my intention by this statement to relegate the technic to terminal anesthesia. Many cardiac cripples can be carried along for several hours with continuous caudal analgesia and with great benefit, particularly when the labor is premature. Also, in some chronic constitutional diseases where pain relief is required over a period of several hours, this technic has seemed to us to be ideal. It is in these patients that continuous caudal analgesia fills a niche that no other method can surpass. On the other hand, caudal analgesia plainly is not indicated in a patient who obviously will deliver in ten or fifteen minutes, because it takes at least that long to establish the analgesic level. The patient is told not to bear down while the caudal analgesic is being administered and then, as the proper level is reached, the baby is born. In these patients the use of inhalation gas or spinal anesthesia is far more satisfactory. I am opposed to classifying caudal as a terminal analgesic, but I am equally opposed to its use for protracted labor. Knowing when to give caudal analgesia is the most important factor in its use. We have for several years been cognizant of the inadvisability of giving continuous caudal analgesia early in the labor, although the general im-

pression among members of the medical profession is that it can be given for long periods of time. During the past two years we have judiciously used sedation, followed by caudal, if we expected three or four hours of labor to elapse before delivery in patients without complications. For shorter periods of time, or if delivery was imminent, a single dose of a spinal or inhalation anesthetic is recommended.

3 Hypotension was one of the most frequent observations noted in our early studies. We believe that this complication has been overcome by the use of the treatment previously outlined.

4 Total spinal anesthesia is no hazard if the precautions set down early in our study are followed. On several occasions we have used the caudal canal for spinal anesthesia when the dura was accidentally tapped.

5 We believe the use of oxygen in all forms of regional block is important. The replacement of body fluids and the use of vasopressor drugs are adjuncts which should not be overlooked.

6 As in saddle block, the necessity for the use of low forceps is increased and posterior positions occur with more frequency. However, we do not believe this is an objection as we practice prophylactic forceps, and rotation of posterior positions is easily accomplished with a well relaxed pelvic floor.

8 The immediate establishment of respirations in the newborn child, especially in the premature infant, the decrease in blood loss in the mother, and the shortening of labor are some of the other advantages which have been amply shown.

9 During the past two years we have used the ureteral catheter technic in almost all of our patients, preferring it at the present time to the use of the malleable needle or the drip method.

10 No postdelivery neuropathies and no serious residual neurological complications occurred while this problem was under study during the last six years.

11 This method has opened the door to successful treatment of some cases of eclampsia and cardiovascular peripheral disease.

Finally, I feel that this method deserves acceptance by the profession as an addition to the many methods now used in the control of pain in childbirth, but that it should be used only in selected cases and by individuals properly trained, and under proper surroundings. The adverse criticism which this technic has received is, I believe, due to several factors. The publicity which it received in its early stages and unwarranted claims seriously impeded its proper study and evaluation. Much of the criticism has come from persons who have not given it a fair trial. Indeed, many of those who have criticized it most severely have never seen it used. The time-consuming element in its use makes it impossible for

the obstetrician practicing obstetrics and delivering patients in several hospitals to even think of trying it. The busy obstetrician often finds it much easier to use other methods which do not require his attendance continuously in the labor room.

I know of many obstetricians who have a routine so that if a patient goes into the hospital, a sedative is given and he is called when the head is on the perineum. This is not my idea of good obstetrics. Continuous caudal analgesia in obstetrics has been shown to be particularly advantageous to the baby. It has been an important factor in the present steady increase in the use of the other forms of regional anesthesia. There is no specialty in medicine where individualization of the patient and the careful selection of the method of pain relief used is more important than in obstetrics. I do not feel that to have a set routine for every patient because it fits in with one's surroundings is the proper method of controlling the pains of childbirth. After studying this problem for six years and having observed several thousand patients delivered by this method, I believe it will survive and become an integral part of our obstetric practice but only when used under the conditions that have been continually stressed in all of our communications.

SPINAL ANESTHESIA

Abdominal Delivery—I should like to divide my discussion of the present status of spinal anesthesia in obstetrics into its use in abdominal and vaginal delivery. The history of the use of spinal anesthesia in surgery and in obstetrics is one that is quite typical of new innovations in medicine, condemned by one group, accepted by another, and quietly bypassed by still another. In 1898 August Bier had 20 mg of cocaine introduced into his subarachnoid space and thus gave to the medical profession a successful clinical technic of spinal anesthesia. This of course was preceded by Corning's unintentional use of spinal anesthesia, and Quincke's description of lumbar puncture. In 1899 Rudolph Matas of New Orleans first employed spinal anesthesia in surgery. The same year, Johnson introduced it in Canada. In 1900 Kneis of Germany first used it in obstetrics. In 1905 novocain was substituted for cocaine by Einhorn. Since its introduction approximately forty-eight years ago there probably has been no procedure which has been more alternately opposed and advocated. During these many years the names of Baba, Pitkin, Vehis, Maxson, Lemmon and, particularly in obstetrics, Cosgrove, have been associated with its use.

In 1930 Cosgrove reported the first large series of patients delivered under spinal anesthesia. The perseverance of Cosgrove, and the introduction of other forms of regional block such as continuous caudal, I believe

partially account for the present revival of its use. In addition, the method of Lemmon known as continuous or fractional spinal anesthesia, and the availability of drugs of less toxicity, such as procaine, metycaine, pontocaine and nupercaine, have played a part in the present day successful use of regional anesthesia in obstetrics. Another important factor is the use of much smaller doses, particularly when the fractional method is used. Cosgrove first pointed out that it was unnecessary to give such large doses as advised earlier by Pitkin, and he supplanted Pitkin's original large dosage by 75 to 100 mg of procaine in the second stage of labor. When Hingson and I were making our observations on the use of continuous caudal analgesia, we tried to determine the smallest intraspinal dose of either metycaine or procaine which would give good anesthesia for both cesarean section and vaginal delivery. It is interesting to note, as we have reported elsewhere, that some patients had no sensation of pain during cesarean section and continued to have some control of the motor pathways on a dose as small as 15 mg of metycaine in Ringer's solution. We believe the giving of the drug between the first and second interspaces instead of between the third and fourth had some bearing on our results.

We abandoned the use of spinal anesthesia in cesarean section in the late twenties because of numerous reports in the literature of sudden deaths from its use, and because in one year in the city of Philadelphia, three patients died before the operation was even started. At that time we were cognizant of the fact that the baby did very much better when the mother was not given a general anesthetic for cesarean section. We therefore attempted to use local anesthesia for cesarean section whenever possible. Our results were satisfactory, but, as I have pointed out many times, only a certain type of individual is adaptable to the use of local anesthesia. What is more important, this type of anesthesia should only be used by certain operators, otherwise it becomes vocal instead of local.

After extensive experiments on monkeys, Lemmon introduced his continuous or fractional technic in 1939. He proved that a single dose of any drug given to these animals as an intraspinal anesthetic was practically always fatal, but when it was administered in small doses the animal could be kept insensitive to pain for twenty-four hours. Since that time we have employed this technic in cesarean section with excellent results. Up to the present writing our series of cesarean sections performed under fractional spinal anesthesia total more than 1000 cases and to date there has been no maternal death. To this might be added Hingson's series in Memphis of 400 patients and equally good reports from numerous other clinics.

The late Doctor DeLee of Chicago, who was the first to recognize the hazards of spinal anesthesia, was its leading adversary. Greenhill still adheres to the principles of DeLee along these lines. In a recent personal communication, however, Andros of the Chicago Lying-In Hospital stated that nine out of ten of their cesarean sections are now being performed under spinal anesthesia, and approximately 68 per cent of their vaginal deliveries are managed under the saddle block technic. I am reminded by this change of my condemnation of the method for many years, but fortunately I have had opportunities, in writing and speaking, to retract many statements which I had made concerning its use. I hope that many of the present day opponents of the use of spinal anesthesia will eventually do the same.

It is true that in the use of spinal anesthesia the patient is exposed to certain hazards, but, just as in the use of continuous caudal analgesia, if the proper technic is strictly adhered to, these hazards are minimized. Occasionally serious complications such as hypotension do arise and some neuropathies have been reported which were attributed to the use of spinal anesthesia. However, in the absence of these complications, our experience with this type of anesthesia demonstrates that in most instances an error in carrying out the procedure was the causative factor in the development of the complication. We feel that the marked decrease in the dosage of the drug used, the fractional method of administration, and the success with which it has been employed in our hands, has been responsible for much of the progress that has been made in the use of spinal anesthesia in cesarean section.

That steady improvement has been made with the use of better drugs and more refined technic is brought out by the fact that in the year 1921, when Gaston Labat established a department of anesthesia in the Mayo Clinic, only one spinal anesthesia was given, while 11,000 spinal anesthetics were administered in the year 1944. The fractional method of administration has been criticized but we believe it to be superior to the single dosage if one is trained in this technic and follows the precautions outlined.

For the past year or two, in our gynecological surgery, we have been employing, in conjunction with fractional spinal anesthesia, an intravenous drip of 0.5 per cent pentothal sodium in glucose, started as soon as the proper level of anesthesia has been established. In the last 100 or more cesarean sections we have been using a modification of this combination. We allow the drip to run at a rate of 45 drops per minute until the baby is removed from the uterus and at that time increase it to 90 drops per minute. This causes the patient, who is already relaxed but not unconscious, to sleep during the remainder of the operation. Until the

actual delivery of the child the mother has sufficient sedation from the pentothal to relax her, yet she is aware of what is going on about her. This amount of pentothal has no effect upon the child. Although I personally have not accepted some of the modern concepts of the psychological effects on the baby of various new methods employed, I do believe that it is most important to relieve the mother of the suspense of wondering whether the baby is alive and well. The baby's cry and reassurance that it is all right allows her to sleep peacefully during the delivery of the placenta and repair of the uterus and abdominal wall but, as she has received only a moderate dose of pentothal, she is awake upon her return to her room.

Space does not permit me to do more than enumerate several factors which have particularly impressed us in the use of this type of anesthesia in cesarean section. Excellent relaxation makes the operation, particularly of low section and extraperitoneal type, much more easily performed. In practically no instance is resuscitation of the baby necessary. The amount of blood lost is much less than under general anesthesia and the contractility of the uterus is more pronounced. Although we routinely give oxytocic drugs, we did manage a fairly large series without the use of this medication and discovered that the uterus responded to the manipulation of repair of the myometrium. The smooth convalescence of the mother is one of the outstanding features. We allow these patients to take food early in the puerperium and the number of postoperative complications, such as distention, nausea, vomiting and ileus, has been minimized. Headaches do occur but we have seen none of great severity and practically all respond immediately to the application of either a wasp girdle or a tight binder applied to the epigastrium. These patients are allowed out of bed on their fourth or fifth postoperative day and are usually discharged on the ninth or tenth postoperative day. A detailed report of our experience with fractional spinal anesthesia in cesarean section is being compiled.

Vaginal Delivery—The excellent results obtained for both mother and baby by the use of the various forms of regional block has brought about a decided increase in the number of our vaginal deliveries performed under spinal anesthesia. This increase is due also to the fact that continuous caudal analgesia of necessity is more difficult and time consuming and requires more meticulous execution of the technic. That there has been a tremendous increase in the number of parturients delivered under spinal anesthesia is again proved by the number of reports that have been presented during the past year. The general consensus of those who have reported large series of cases delivered in this manner seems now to present a fairly definite pattern.

Just as in continuous caudal analgesia, saddle block is not designed to

relieve the pains of early labor and here again the early first stage of labor should be managed by the use of drugs selected for the individual patient. Although some clinics are at variance as to the proper time to give the spinal anesthetic, it is fairly well agreed that the maximum length of time that a patient can be carried with a single injection is probably two or three hours before delivery. Although many men advocate the repeating of the spinal anesthesia, to me this would seem to increase slightly, but definitely, the hazards of the technic. When spinal block is instituted there should be cervical dilatation of at least 5 or 6 cm and the contractions of the uterus should be of good quality, occurring at intervals of four or five minutes. It has been our frequent experience that the preliminary sedation given during the first stage of labor will carry the patient practically to the terminal stage, at which time delivery is easily accomplished under spinal injection. As suggested by the Chicago Lying In Hospital group, for those who are not exceptionally experienced in the use of the block technic it would seem wise to limit its use to the semiterminal stage.

It is not my intention to discuss here in detail the technic of spinal anesthesia in obstetrics. At the present time we are using heavy nupercaine in glucose solution if we desire the block to continue over a period of two or three hours. For the terminal stage and delivery we have employed metycaine, and procaine, usually in 35 mg doses. In most instances this gives satisfactory relief of the terminal pains and permits delivery with outlet forceps and episiotomy. Great care should be exercised in preventing the anesthetic level from rising too high. This can be controlled by tilting the table. Frequent, careful blood pressure readings should be made.

If one of the longer acting drugs is given for delivery, the level of anesthesia should be carefully noted before the patient leaves the delivery room. On one or two occasions we discovered, after the patient had been returned to her room, that the level of the still active drug had risen. We believe this to be an important observation. Patients in whom a fairly high level is sustained at the end of an hour, when they are taken from the delivery room, should be watched most carefully. Our rule is that the resident or nurse anesthetist must chart the level of anesthesia, blood pressure, pulse, and height of the fundus of all patients when they are taken from the delivery room. Should the effects of the anesthesia be completely worn off at the time of removal from the delivery room, the patient is made comfortable by a hypodermic injection of morphine. This is particularly true if the effect of the sedative has also worn off.

Frequently the presenting part is at the vulvar orifice while the patient is still under the effects of the preliminary sedation. These patients may be delivered under spinal anesthesia. Even though they are restless

before the spinal injection is given, they will immediately quiet down following the procedure and will sleep through the delivery and for some time afterwards. These particular patients should be watched even more closely than those who are markedly alert, as in the former it is sometimes difficult to ascertain the exact level of anesthesia. In using small doses of drugs such as metycaine or procaine, we have not encountered any difficulty. It is our belief that the longer acting drugs should never be given for immediate delivery and particularly to a patient who is not completely orientated.

The advantages of vaginal delivery under spinal anesthesia are approximately the same as under continuous caudal analgesia. Outstanding among these are excellent relaxation of the pelvic floor, particularly in posterior positions necessitating rotation, the immediate establishment of respirations in the newborn, and the diminution of blood loss in the mother.

The usual contraindications to the use of spinal anesthesia should be strictly observed.

The number of postspinal headaches have not been sufficient to impress anyone connected with our Clinic but they do occur, and occasionally one will be rather severe and continue for a period of several days. We have found that, as in the control of postoperative headache following cesarean section, the application of the wasp girdle or the insertion under the binder of a rubber bladder which is distended with air to make pressure, will give the quickest relief. As in our rather large series of caudal cases, we have had no residual neuropathies following this type of anesthesia. One patient developed foot drop which persisted for several weeks but this complication followed an extremely long labor and difficult delivery. The neurologists were of the opinion that these factors played a more important part in its etiology than did the spinal anesthetic. Strict adherence to proper technic must of necessity be carried out if complications are to be avoided.

The use of regional block anesthesia is of advantage not only to the mother and the baby, but it also plays a role as far as the attending physician and the nursing staff are concerned. This is particularly true in spinal anesthesia, where nursing care is reduced to a minimum. When a patient is making rapid progress and the presenting part is almost visible, the injection of the drug allows ample time for preparation of the patient and permits the physician to carry out his own preparation without haste and confusion. We make it a general rule that when low forceps are applied the traction is made simultaneously with the uterine contraction and the patient, whose bearing-down reflex is lost, is asked to aid in the delivery by the use of her abdominal muscles. Sometimes in low transverse arrest one blade of the forceps is applied to the side of the head

from which the rotation should occur, and with the contraction of the uterus and the patient bearing down, the single blade helps in rotating the head into an anterior position, when the other blade may be applied.

The third stage of labor under spinal is quite similar to that under other forms of regional block anesthesia. Because of the increased irritability of the uterus, some writers caution against the use of oxytocic drugs when delivery is managed under regional block. The likelihood of trapped placenta is a possibility. We have continued the use of ergonovine intravenously when the anterior shoulder impinges under the pubic arch and pitocin is given as the placenta is removed. So far we have not had difficulty with trapped placentas although this complication must be kept in mind. The excellent results which we have had with this method of stimulating the uterine contractions has undoubtedly been an important factor in the decrease in the amount of blood loss.

In all forms of regional anesthesia we routinely have the patient breathe 100 per cent oxygen from the time she is put on the delivery table until the cord is cut. Walter C. Rogers of Pasadena, California, in a report of 5000 vaginal deliveries recently published in the *Western Journal of Surgery, Obstetrics and Gynecology* (56 (4) 237-238), points out the importance of control of the level of anesthesia and agrees with Eversole that in spinal anesthesia it is not the anesthetic agent which is dangerous but rather the careless anesthetist. To have careful administration is far better than giving antidotes. He also reports a 5 to 10 per cent incidence of postspinal headaches which lasted from two to five days and a few patients whose headaches lasted fourteen to sixteen days.

CONCLUSIONS

The use of these two methods of pain relief in obstetrics has been criticized severely by those who probably were not in a position to speak with authority. It is only by reporting many large series of patients managed with these techniques and giving an honest evaluation of the results obtained, that these methods can attain their rightful place in obstetric practice. In spite of all the adverse criticism, it seems to me that by reason of its advantages, regional block has been definitely established. If used properly these methods are a valuable adjunct. In most instances the modern American woman demands some relief from the pains of childbirth and this is quite understandable. It is, therefore the duty of all of us who are interested in this specialty to give her this relief, if it can be obtained without jeopardizing herself or her unborn child. Although we have probably not arrived at the zenith of pain relief in childbirth, during the past decade we have certainly made steady progress toward our goal, and can report improvement.

BEDSIDE CARE OF THE NEWBORN BY THE PARTURIENT MOTHER

THADDEUS L MONTGOMERY, M D , F A C S *

UNDER natural circumstances the process of parturition among mammals proceeds in the following fashion. The expectant mother withdraws herself from the other members of her group, selects a quiet protective spot in which to deliver her offspring, and then gives birth unaided and untouched by any of the group. The newborn is expelled spontaneously, not always without accident or stillbirth, but at least with respiratory center uninhibited by anesthetic or analgesic agents. It squeals, barks or mews, as the case may be, and quickly clears its lungs of amniotic fluid. The cord continues to pulsate until the vessels collapse or until it is torn or chewed away by the mother.

The newborn crawls or toddles to the side of the mother, seeking the warmth of her body and searching for nutrition at her mammary glands. Thus the act of nursing is inaugurated at once. During subsequent days the newborn calls for milk at the breast whenever it is hungry, and the mother gives freely of her supply at almost any time.

Soon after delivery the parturient is up and about searching for food and looking out for the welfare of her offspring. Within a few days she and her litter return to the flock, but the interdependency of the offspring and the mother continues until the offspring is able to assume the responsibilities and necessities of living for itself.

It is hardly necessary to point out the many ways in which this natural process of reproduction has been modified in the human being, particularly under the influence of 'civilization,' by the present ideas of pain relief in labor, and by the concept of care of mother and baby in maternity hospitals. However, it may be safely asserted that many of the principles of physiology which have been perfected through thousands of years for the safety and efficiency and preservation of animal life are thwarted by some of the procedures which we choose to include in modern obstetrics. Attention is called especially to the interference in normal baby-mother relationship which has developed in hospital care of the parturient.

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With the increased use of analgesic and anesthetic agents it has become the custom to separate the baby from its mother upon the act of delivery. In some instances the mother is so deeply under the influence of analgesic or anesthetic agents that she does not recall having delivered herself, could not recognize her baby if it were shown to her, and would be unable and unresponsive to any effort at breast feeding after delivery.

Sometime later, perhaps twelve or twenty-four hours, the baby is presented to her as her own. At intervals of six or eight hours the baby is brought to her room for a brief inspection and application to the breast. After lactation begins the breast nursing is placed on a fixed schedule of every three or every four hours, quite arbitrarily and quite independently of the individual desires or interests of the newborn. The remainder of the time the baby is kept in a centralized nursery in which there may be housed ten, twenty or thirty babies arranged in regimental rows in a room of varying dimensions and usually inadequate size.

In many other cases for one reason or another the baby is not nursed at the breast at all, and the contacts of mother and baby during the hospital stay are further reduced. At the conclusion of some five or ten days the mother is presented with her baby and a formula for its feeding, and is discharged to face alone a host of new and unusual situations as best she can.

Today 95 to 99 per cent of the babies in large cities are delivered in centralized institutions, most of which were constructed for the care of the sick and only modified in slight degree for the care of the parturient. So rapid has been the growth of hospital practice of obstetrics that it has been impossible to cope adequately with the demands for hospital maternity beds, and our institutions have been overcrowded and undermanned.

Infectious disease, especially of the skin, gastrointestinal and respiratory tracts have appeared, and with distressing increase of frequency serious epidemics of infectious diarrhea have been reported from all sections of the country. In many of these the mortality among the babies has been quite high. Efforts to overcome these untoward developments have taken the direction of amplification of nursery facilities, the establishment of rigid rules for the care of the newborn, and the insistence by Boards of Health upon increased hours of nursing care per individual baby. These efforts, however, have not been successful, for hospital construction like all forms of building lags far behind the needs of the situation, and there have not been enough of trained personnel during and since the war to fulfill the nursing requirements of the new and rigid regulations. Procedures that were set up for the centralized nursery were so exacting that breaks in technic were bound to occur, and such broken links proved often the source of trouble.

Because of these factors which have to do with the safety of the newborn obstetricians and pediatricians in various sections of the country have been considering the idea of doing away with the central nursery. Barnett³ reported his experiences with the rooming in arrangement for newborn infants in a small hospital. Jackson, Thoms and others¹¹ have established a rooming in unit for four newborn infants. Montgomery, Steward and Shenk¹² reported recently their experience with over a thousand babies roomed at the bedside of the mother. Many of the hospitals of continental Europe for generations past have housed the baby with the mother. Perhaps the first effort to adjust hospital architecture to this new concept has occurred at the George Washington University School of Medicine under McClendon and Parks.² There has even been some suggestion among obstetricians and pediatricians of returning to home delivery in an effort to avoid the ravages of infectious disease of the newborn.

In addition to these factors which have had to do primarily with the health of the infant, other angles of the problem have attracted the attention of pediatricians and psychiatrists. These have to do primarily with the disturbance of the normal and natural relationship of baby and mother which has taken place in hospital care, and the subtle effect which such separation may have had upon the future development of the child. Maloney, Montgomery and Trainham in Detroit¹ call attention to this point. They have founded the so-called Cornelian Corner,^{9, 10} the idea of which is to restore to the mother the companionship of her baby, to encourage breast feeding and to surround the baby with the affection and intimate maternal care which seems to them of such importance in early development.

In view of these several observations the policy of rooming the normal full term newborn baby with its mother was inaugurated in the Jefferson Medical College Hospital on July 12, 1947. The primary reasons for so doing were two in number first, the fear of contagious disease among the newborn housed in a central nursery, and second, the impossibility of securing a sufficiently large corps of trained nurses to provide adequate care for babies day and night separate from their mothers.

In addition to these two considerations we suspected that the separation of mother and child immediately after delivery was interfering with the normal physiologic relationship between the two, and also impairing the function of breast nursing.

From July 12, 1947, until the present time, May 15, 1948 there have been approximately 1200 newborn babies roomed with their mothers at the bedside. While our hospital was not designed with this arrangement in mind, yet actually the architectural features of the obstetrical wards lent themselves quite well to the new project. The obstetrical wards con-

sist of six rooms of six beds each, each of which is provided with a toilet, a wash basin, adequate heating and good ventilation. There is ready visibility from one ward to another and from the wards to the adjacent corridor. The wards and other rooms of the obstetrical floor are arranged around a central office. Personnel, including physicians, nurses and junior clerks, circulate through the wards and corridors freely during the day and not infrequently at night so that the mothers and their babies are under adequate observation.



Fig. 208.—Crib wardrobe.

Normal, healthy, full-term babies are placed with their mothers very soon after delivery. If the baby has considerable mucus and there is any question about its condition the baby is retained in a nursery for a few hours until circumstances warrant of its being put by the mother's bedside. Occasionally when delivery is at night the baby is not placed with the mother until the next morning.

By process of trial and error we have found that there is certain equipment essential for the care of the individual baby by the mother's bedside. For this purpose we have designed what we have chosen to call a crib-wardrobe (Fig. 208) which is attached to the end of the baby's crib.

and contains the diapers, solutions and other necessities for the care of the baby and of the mother's breasts. These have been built for us by the hospital carpenter at a minimum of expense, and they work quite efficiently. They can readily be removed from the cribs, are readily washed and cleansed. They are within easy reach of the mother while she is in bed or while she is sitting in a chair at the side of her baby's crib (Fig 209). Such an arrangement permits not only of ready access to material but also provides an individual sterile supply of materials for each baby, untouched by any one else except the mother herself.



Fig 209.—Baby and equipment at bedside of mother. (From Transactions of the American Gynecological Society, Williamsburg Va., May 20 1948.)

Placement of the baby's crib by the mother's bed is maintained both night and day, unless one or the other is ill or unless the baby is unusually restless or crying. These latter cases, however, are quite exceptional.

During the first twenty four hours the nurses devote a great deal of time to the instruction of the new mother in the care of her baby. They teach the mother the technic of breast nursing, how to cleanse the baby and change the diapers, and the signs of trouble to watch for. During this first twenty four hours the mother does little more than learn about the care of the baby and observe its progress. After the first twenty four hours, however, the mother is out of bed and ambulatory, is able to come

and go to the lavatory, takes care of herself rather completely, and takes almost complete charge of the care of her baby

Each morning the nurses assigned to nursery duty make rounds through the wards with a ward carriage equipped for the weighing of the baby, changing of the dressing of the cord, and recording of temperature. Each mother is provided with a bath pack which contains the materials for the redressing of her baby, redressing of the crib, and a fresh supply of diapers for the day. These she handles herself and prepares her baby for weighing and examination as the ward carriage comes along. Records are collected at this time of the baby's progress, weight gain, number of feedings and so forth, and the baby is carefully inspected by the supervising nurse of the nursery. Dry technic is employed in the care of these babies and only the areas in the folds of skin and around the anus are cleansed with sterile water and a cotton swab.

Subsequently the supervising nurse of the nursery makes rounds twice every eight hours. Other nurses are always on hand or within ready call, to help the mother with her baby at any time.

Mothers are encouraged to nurse their babies. In many instances the baby is placed at the breast in the delivery room at which time the mother is permitted to see and fondle the newborn and receive her first lesson in breast nursing. This seems to meet with the approval of the newborn for his wailing usually ceases and he takes to the breast with avidity. Subsequent nursing is on a so-called "demand" schedule.^{4 5 6 7} During the first two or three days of life it is at rather frequent intervals and the mother is instructed to nurse the baby for only five minutes. She is also given sterile lactose water to provide the baby if its demands are too great and too frequent. After the milk comes in the schedule of breast feeding settles down in a rather natural fashion to about every three or three and one-half hours. However, with the baby at the bedside the rule is to feed the baby when it is hungry and not according to any preconceived hospital regimen.

From the foregoing it may be realized that both early ambulation and breast feeding are important factors in the success of the rooming-in project, and it may also be stated that the rooming-in project is a stimulus and an encouragement to lactation and also an important factor in furthering involution. These mothers seem to recuperate more rapidly and are in a much better state of health when they leave the hospital on the fifth day than they were formerly at the tenth or eleventh day.

The husband of the ward patient is permitted to see his baby soon after delivery and then to visit two evenings a week. Since the baby is discharged on the fifth day this does not impose any special hardship. In the case of patients in one of the low cost semi-private wards included in

this rooming in project the mother and husband of the patient are allowed to visit twice a day. The visitors wear gowns and the husband is permitted to wash his hands and hold the baby if he so desires.

OBSERVATIONS

Our experience with the rooming in project has been too brief to allow any categorical statements regarding its success or failure. However, there are a number of observations of interest which have accumulated, and the impression is growing in our department that the method is a happy solution to many of the problems of hospital care of the newborn.

In the first place, of the some 1200 babies that have been housed with the mother during the period of time mentioned there have been no instances of diarrhea or impetigo. There was only one questionable case of respiratory infection which was proved to be nonexistent after careful study by the pediatrician. However, we realize that infection will inevitably occur in one of these babies at some time in the future but we feel much better protected than formerly in view of the fact that the room in which such infection occurs can be closed, that only five other babies in that single room have been in any way exposed to the infection. Quarantine of the one room can be carried out until all six babies are discharged. The one ward room can then be cleansed and no further admissions permitted until such procedures have been carried out. This seems a much safer arrangement than the old plan where some thirty to thirty five babies housed in a central nursery were all exposed if one baby became ill.

None of the babies have had serious disturbances at the mother's bed side. Occasionally a baby chokes slightly after breast or bottle feeding, in which instance the mothers are instructed to turn the baby on its side, pat it gently on the back, and call upon the nurse for assistance. Facilities are available for prompt suction and administration of oxygen if necessary. There were two or three instances in which this has had to be done and in all such cases the symptoms have been recognized very early by the mother, probably much earlier than they would have been recognized in the central nursery, and all of the babies have recovered promptly under appropriate treatment.

In addition to these factors which have to do directly with the health of the baby, it has been noted that these babies at the bedside of the mother have seemed more contented, cry less, and gain more rapidly in weight than when the babies were kept in the central nursery. When a baby cries the mother reaches out from her bed or chair, inspects the baby to make sure that its diaper is dry, and feeds it if it is hungry. In almost all cases this takes care of the situation and the crying subsides.

The attending physicians, nurses, and visitors have remarked how quiet the wards are and how little crying of the baby is noted. Certainly there is nothing which is comparable to the pandemonium which reigned in a central nursery for an hour or more before the next scheduled feeding time. From our point of view, therefore, the progress of these babies has been quite satisfactory.

As far as the nursing care of the baby is concerned, here too there has been a decided improvement, for under the old regimen we had not enough nurses to properly supervise and observe the babies in the central nursery at all times. Now we find with the present rooming-in project that the same number of nurses, or at least the same number of nursing hours, are sufficient to care appropriately for both mother and baby. There are two reasons for this. First, with early ambulation the mother is able to take care of herself after the first twenty-four hours except in particular and special cases. In the second place, with the baby at the bedside the baby receives practically twenty-four hour constant observation and supervision from its mother, and this we consider far better than we could provide with even a large corps of graduate nurses. As a result of this policy we have been able to concentrate graduate nursing care upon those patients in the department who particularly need such care, i.e., the ill mother or the antepartum patient with complications, and the premature baby who still must be housed in the central, specially prepared, and adequately staffed premature nursery.

The presence of the baby at the bedside seems to stimulate interest in breast feeding on the part of many mothers who might otherwise be reluctant. Eighty-three per cent of our ward patients consistently are nursing their babies now and about 50 to 60 per cent of the semi-private patients who occupy the low cost semi-private ward. On the schedule of demand feeding 25 per cent of the babies have regained their birth weight by the fifth day, which is the usual time of discharge from the ward. Of those full-term ward babies which have been followed in our own well baby clinic 83 per cent were still nursing at the breast for one or more months after delivery.

The final question which always arises in reference to the rooming-in project is, Do the mothers like this arrangement? This is a difficult question to answer unequivocally. Since this project has been established as the rule in the ward service, patients admitted to the Division of the Department of Obstetrics and Gynecology have had to accept the procedure as a part of the hospital routine. However, most of them have done this with more interest and enthusiasm than a mere compliance and most of them appear to enjoy the companionship of their baby, take pride in its care, and are jealous of its interests and safety.

All of them obviously learn more about the care of their baby than they ever have before and are in a much better position to cope with the management of their offspring when they return to their homes.

The young first mothers are the most enthusiastic concerning the idea and of course are quick to realize its particular value to them. They leave the hospital with a sense of confidence in their ability to cope with home conditions and with home care of the baby, which is quite different from the attitude before this project was undertaken. Many of the multiparas state that they wish they could have had their babies with them at previous deliveries. Others who have lost much of the enthusiasm for child bearing look upon this care of the baby as an imposition, they have come to the hospital with the idea of getting a rest from home duties and care of babies and would rather not assume the care of the newborn until they again return to their home with the child. However, even in the latter group there is a good deal of the mother instinct which persists and if the baby is moved from the bedside to a central nursery when the reservations of the patient are changed, she manifests a great deal of concern as to what is going on with her baby.

This factor of knowing what is taking place with the baby seems of considerable importance and significance to the mother and it is one point on which there has never been any very satisfactory solution under the old central nursery system. We found that so many mothers were worried about which baby was crying in the nursery during the night and were anxious to know what the pediatrician thought of their baby and of their baby's progress, and were constantly asking about this or that slight defect or blemish that they had noted in the baby during its short period of visitation to the room.

Now with the rooming in arrangement the mother has all of this evidence and information before her. If her baby cries she will promptly find out why it cries. When the pediatrician examines the baby she is there to watch its examination and ask questions concerning its welfare. During the course of the first days of the baby's life, therefore, she can become familiar with its habits and characteristics and is pretty well acquainted with the youngster when she bundles him up and takes him home.

From the standpoint of the obstetrician and pediatrician the arrangement of rooming in of the baby interferes in no respect with their work or activities. As a matter of fact the having of the two patients together provides each of them with a more complete picture of the mother-baby relationship and puerperal progress. The pediatricians naturally, are more than pleased with the progress of these babies, the absence of infection, the excellent care of the newborn and apparent contentment of the newborn, also with the higher percentage of breast feeding. They

find, too, that when these mothers go home there are fewer calls about incidents and trivialities which bother the new mother no end when she has the full responsibility of her baby suddenly imposed upon her

The question has not been completely answered as to how this project will work in private and semi-private rooms. It has been undertaken quite successfully in a few instances in our own department, but not on a very extended scale. However, we have been sufficiently impressed with the practicability and the workability of the idea to now secure the additional material necessary for the inauguration of this plan in private and semi-private service where it will soon be undertaken.

SUMMARY

Some 1200 babies have been housed with the mother during the past ten months in the obstetrical ward service of the Jefferson Medical College Hospital. From the standpoint of the newborn this arrangement has proved quite successful inasmuch as there has been no contagion, no illness among these babies, and the babies have gained nicely in weight and seem quite contented at the mother's bedside.

The mothers have in general enjoyed having their babies with them. They have learned to take care of the baby at an early date in the hospital and have left the hospital with a new sense of confidence in their ability to continue with baby care at home.

It has been found that early ambulation and breast feeding adapt themselves nicely to this program and that the program itself is an incentive to lactation and an encouragement to involution and early regaining of strength on the part of the mother.

The arrangement has worked particularly well on the ward service where there are six-bed rooms and in which mothers can watch each other, teach each other, and can be under the frequent observation of nursing personnel.

The question of whether the plan will work successfully in the private and semi-private rooms has not been completely answered but there seems no reason to think that the special problems of this phase of the service cannot also be solved on a similar basis.

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ADDITIONAL ARTICLES

MEDICAL MANAGEMENT FOLLOWING VAGOTOMY FOR PEPTIC ULCER

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THE literature concerning the treatment of peptic ulcer by vagotomy is accumulating rapidly. It is our purpose to present the problem confronting the physician when the patient comes into his hands following vagotomy for peptic ulcer. It is based on a two-year experience at the Johns Hopkins Hospital.

CLINICAL OBSERVATIONS

Simple Vagotomy—This group of patients includes those in whom vagotomy was performed alone or in association with suturing of a perforated peptic ulcer. In these patients, disturbed gastric physiology is encountered. Secretory tests demonstrate decreased psychic and nocturnal secretion. X-ray studies reveal gastric dilatation, decreased peristalsis and delayed motility, while antral atony, patulousness of the pylorus, and negligible mucosal changes are noted gastroscopically.^{1, 2}

Vagotomy with Gastroenterostomy—The x-ray gastric changes are as noted in simple vagotomy. The mucosal changes seen gastroscopically, when present, are relatively mild.² Symptoms, to which reference will be made, are less pronounced than in simple vagotomy or in vagotomy with subtotal gastrectomy. This is probably due to an adequate gastrojejunial outlet in an otherwise intact stomach.

Vagotomy with Subtotal Gastrectomy—X-rays reveal relatively rapid emptying of the residual gastric pouch, and dilatations of the jejunum contiguous to the stomach. Edema, hypertrophy, erosion, friability of the residual stomach with dilatation and relative inactivity of the stoma may be seen with the gastroscope. As time goes on, the tone and function of the stomach approach the normal state. However, the mucosal changes appear to be permanent, although they may fluctuate in degree.^{1, 2} Here the symptoms are more pronounced than in simple vagotomy because of the more marked anatomic and physiologic changes.

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Influence of Vagotomy on Other Organs — Intestine After vagotomy, x-ray studies suggest that the upper jejunum may be slightly dilated, its folds coarsened, and its motility impaired. The colon appears unaffected.³ Following kymographic studies Moore and his associates concluded that motor changes beyond the pylorus are transient and ill defined.⁴

Gallbladder — In the vagotomized laboratory animal, the ability of the gallbladder to contract following duodenal instillation of cream, fatty acids, casein, skimmed milk and peptone is not affected. However, the latent period is prolonged. The response of the gallbladder to cholecystokinin is unaffected by vagotomy.

Pancreas — There is no clear evidence that pancreatic function in man is altered,¹ although Orr and Johnson⁵ believe that pancreatic secretion is slightly reduced by vagotomy.

THE PROBLEMS

From the standpoint of the ulcer, vagotomy alone or in combination with other operative procedures presents certain unquestioned advantages. If the operation is performed under the proper circumstances, heartburn, indigestion, gnawing pain and acrid regurgitation are usually abolished. The operation is also advantageous from the standpoint of the patient. His appetite is good, he can eat anything, his vitality improves and he is able to resume his usual occupation. He is usually no longer constipated. Probably because of these changes, the patient's mood improves.

Certain difficulties follow vagotomy. Varying degrees of chest pain may occur if the operation for vagotomy is transthoracic, but this subsides in a few weeks. Diarrhea, transient and rarely very troublesome, disappears. Fullness, regurgitation, and nausea with or without emesis may be distressing, these tend to diminish and eventually disappear in most patients. Regurgitation is often annoying, it is no longer acrid. It is said to be foul, but the odor is not to be detected by the examiner or bystanders in our experience. In addition, two other syndromes appear when subtotal gastrectomy or gastroenterostomy is performed: the "dumping" syndrome, and hypoglycemia. They may occur independently or concurrently. Their significance is not often fully appreciated. The dumping syndrome and hypoglycemia are not caused by vagotomy per se, as they may be seen in patients with gastroenterostomy or subtotal gastrectomy without vagotomy. They account for some of the failure ascribed to vagotomy. Although reoperations for relief have been performed, these are ordinarily unnecessary, for the symptoms are amenable to medical management.

The *dumping syndrome* is characterized by upper abdominal fullness

and discomfort, anxiety, weakness, sometimes nausea, with or without vomiting, and occasionally sweating. It comes on during or within one-half hour after eating. The consensus is that the dumping syndrome is due to the distention of the proximal segment of the efferent jejunal loop. This distention is brought about by the rapid arrhythmic ejection or 'dumping' of gastric contents because of the absence of a sphincter at the stoma. The reduced size of the gastric pouch in subtotal gastrectomy is a contributing factor to rapid emptying. Another view, not generally accepted, is that these symptoms are due to postprandial hypoglycemia, a phenomenon of the 'postgastrectomy state'.

The *hypoglycemia syndrome* is characterized by sweating, nervousness, weakness, drowsiness, hunger, pounding of the heart, and sometimes even prostration and a sense of impending syncope. It usually occurs two hours after the last meal. The patient often describes the symptoms as coming on 'just before eating'. Physical exertion increases the severity of the attacks. An oral glucose tolerance test generally reveals an abrupt incline to a peak, ordinarily in half an hour, but occasionally in an hour, so that the blood sugar is as high as 200 to 230 mg per 100 cc. In the next hour, a precipitous decline to 50 mg and less is encountered. Not all with this curve have these symptoms in the same degree, in a few they are negligible or absent (see Fig 210).

The symptoms of dumping syndrome and hypoglycemia are similar, but the pathogenesis and temporal relationship to food intake are different in each. In consequence, the management of each syndrome is different.

When digestive or abdominal symptoms recur, not attributable to the dumping syndrome or hypoglycemia, the following two questions arise:

1. *Has the ulcer failed to heal or has it recurred?* This brings up the important problem *Have all the vagal branches supplying the stomach been cut?* It has been believed that complete bilateral severance is a *sine qua non* for successful operative outcome. *How is this to be determined?*

The methods available to ascertain the complete bilateral severance of gastric vagal branches are by means of two secretory tests namely the insulin test and the quantitative estimation of nocturnal gastric secretion.

THE INSULIN TEST This test is based on the observation that insulin induced hypoglycemia stimulates the vagal center in the medulla and in consequence gastric tone and gastric secretion are increased. When all the gastric vagal branches are completely severed, adequate insulin-induced hypoglycemia will not result in increasing gastric acidity. This is the most accurate test available today in ascertaining complete severance of the vagi in simple vagotomy. However, it has its limitations.

especially in subtotal gastrectomy and gastroenterostomy with vagotomy. After these operations the alkaline intestinal contents may regurgitate into the stomach and neutralize any acid present. Furthermore, the gastric secretory mucosa is reduced in extent or completely ablated by subtotal gastrectomy.

DETERMINATION OF NOCTURNAL SECRETION In duodenal ulcer following simple vagotomy, the total twelve-hour nocturnal secretion is usually reduced 50 per cent or more. Failure of such marked reductio shortly

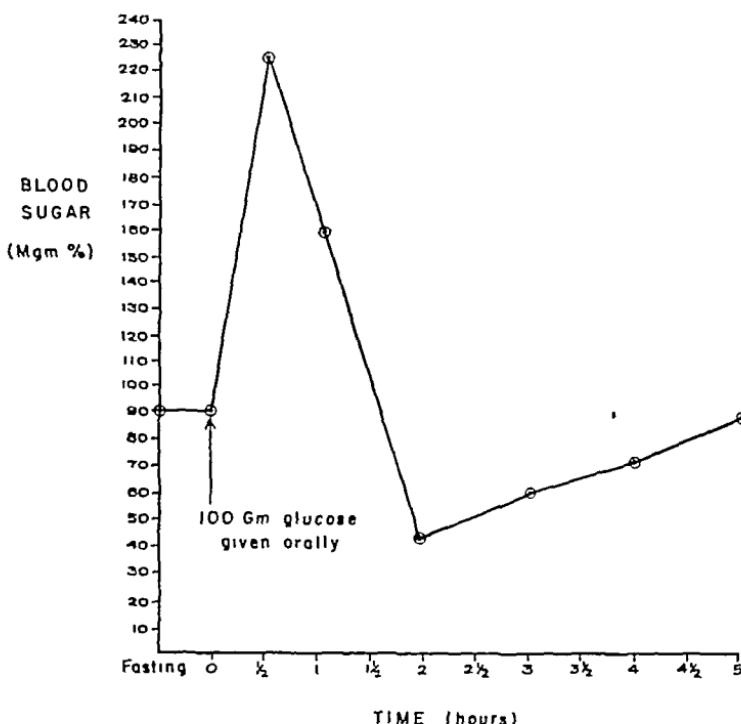


Fig 210.—E R (C-M 31) Oral glucose tolerance test done thirteen months after transthoracic vagotomy followed by subtotal gastrectomy. Symptoms occur at the depth of hypoglycemia in 75 per cent of those with subtotal gastrectomy with vagotomy manifesting this typical curve.

after operation suggests—but does not prove—failure of complete bilateral gastric vagal section. During the first postoperative year, the nocturnal gastric secretion tends to revert to its preoperative level possibly due to gastric autonomy. Obviously, the nocturnal gastric secretion has no place in gastroenterostomy and subtotal gastrectomy.

These measures have been detailed and critically analyzed by us in a previous communication.¹

2. *In what ways may other organs have been disturbed by virtue of this operation?*

In recurring distress, as far as is now known, the function of other abdominal viscera innervated by the vagi are not perceptibly disturbed. However, in gastroenterostomy and subtotal gastrectomy, the dumping syndrome and hypoglycemia, mentioned above, must be considered in the differential diagnosis of recurring abdominal pain or discomfort.

THERAPY

Approach to the Patient.—A proper psychologic approach to the patient is important. Adequate discussion of the problem prior to operation, including its necessity as well as probable benefits and disadvantages, will allay anxiety and facilitate acceptance of the postoperative state.

Dietotherapy—In simple vagotomy and in vagotomy with gastroenterostomy, an unrestricted diet of three meals per day can be taken without difficulty. After subtotal gastrectomy the residual gastric pouch is small, and postoperative gastritis and jejunitis may be present. Five or six smooth feedings are given at the outset. Subsequently, patients, of their own accord, reduce this frequency to three or four feedings and are able to partake of a well balanced routine.

Pharmacotherapy—Pharmacotherapy is based on the simple principle that amelioration of fullness, regurgitation, nausea and emesis depends upon improvement in gastric tone and peristalsis with consequent better emptying. This is often accomplished by the use of the cholinergic drug urethane of beta methylcholine chloride, urecholine (Merck) which stimulates the vagal nerve endings. It has the disadvantage of stimulating gastric secretion, as well as increasing tone and peristalsis but we have seen no ulcer recurrences coincident with its use. It is given orally in 5.0 mg doses three times daily before meals and 2.5 mg doses after meals, usually without untoward manifestations. Two of our patients re-operated upon for gastric retention might have been spared this procedure were this drug available at that time.

Diarrhea is often readily controlled upon the administration of an antispasmodic and sedative for a week or two. Sometimes an adsorbent, such as kapectate, is given for a brief period. Urecholine may be tried in persistent cases to reestablish temporarily some degree of parasympathetic activity of the upper digestive tract. Pancreatin has apparently been effective in some cases.⁸

Therapy of Dumping Syndrome.—The dietetic principle used in the treatment of dumping syndrome consists in the avoidance of bulky foods which would leave the stomach quickly and overdistend the upper jejunum. This may be accomplished by limiting all liquids at mealtime and prescribing four to six small feedings to be taken slowly.

Therapy in Hypoglycemia—Prophylaxis—1. To obviate hypogly-

cemia, a dietary routine high in fat, low in carbohydrate, particularly eliminating the readily absorbable monosaccharides—dextrose and fructose—is given three times daily. Vitamin C deficiency is supplied by prescribing ascorbic acid orally.

2 The principle of six feedings may be utilized. Frequent feedings forestall hypoglycemia by supplying carbohydrate at a time when it might be expected to occur following the previous meal.

3 Any readily assimilable carbohydrate (chocolate, fruit juices, etc.), taken at two-hour intervals between meals, may be adequate.

4 Ephedrine is also used at times to mobilize glucose⁷ but we have had no occasion to employ it.

Curative—At the first manifestation of symptoms of hypoglycemia, sweetened fruit juice, chocolate, candy or similar substance should be eaten.

INDICATIONS FOR FURTHER SURGERY

If the persistent pain, nausea, emesis and regurgitation are due to recurrent ulceration or gastric retention and do not respond to the outlined medical procedures, then the performance of subtotal gastrectomy would be in order. We have seen no recurrent ulcerations in an experience of over two years involving fifty cases of vagotomy, although rare recurrences are reported.

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PHYSICOCHEMICAL CHANGES IN INTESTINAL OBSTRUCTION

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IT is only within the past thirty five years, beginning with the experimental work of Hartwell and Hoguet,¹ that the importance of the physical and chemical factors in intestinal obstruction has been recognized. During this period a great volume of data has been accumulated by inquiry into the various component fields—detailed studies at representative levels of the alimentary tube and investigation of changes in the experimental animal or clinical case as a whole. For several years now the major changes have been described and rational therapy directed toward their correction or control. While many basic problems remain to be clarified and while contemporary or future findings may change concepts now widely held, it seems worth while to present an integrated view of the subject in its present status.

BASIS OF THE PHYSICOCHEMICAL CHANGES

The basis of the physicochemical changes in gastrointestinal obstruction lies in the distention of all or parts of the alimentary tube proximal to the point of obstruction and in the chemical changes incident upon the loss of fluids and electrolytes due to vomiting, lavage or suction drainage before or after surgery. The cause of the morbidity and mortality in obstruction is probably a combination of these factors—distention and loss of fluids and electrolytes—but, in addition, there may be still others, as yet undiscovered, unconfirmed or even presently uninterpreted. Whipple² and his fellow workers found many years ago that if incisions are made across the gut of the dog at two places to create an isolated segment a few inches long with its ends closed off and the continuity of the main portion of the alimentary tract is then restored, death occurs more rapidly than if a simple obstruction is created by ligation at the same level of the gut. Now, undoubtedly, there is a combination of distention and fluid secretion into this isolated segment, but it remains to be demonstrated conclusively whether this explanation of the subsequent morbidity and mortality is adequate or whether there are further factors such as toxic proteoses formed in the intestinal mucosa (as Whipple has

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suggested), serious reflex neurological or enzymatic phenomena, or others

It is certain that simple distention of the bowel can ultimately lead to death, even without a significant loss of fluids or electrolytes. Yet the mechanism here is not fully understood. Taylor³ and his associates placed a balloon in the duodenum of the dog, distended the segment to a pressure of 100 mm of mercury but had an open rubber tube so placed that there was no disturbance of the continuity of the digestive canal, thus there was no appreciable loss of their contents yet these animals exhibited all the phenomena of acute obstruction including exitus. That there may have been a neurological element in this demonstration is indicated by the fact that animals in which the selected duodenal segment was denervated prior to the distention procedure survived much longer. Carrying this over into the field of human medicine we can find the occasional instance of Richter's hernia in which only a portion of the intestinal lumen is cut off from the direct continuity of the canal, this is not a true occlusion yet the clinical picture is one of acute intestinal obstruction.

It must also be borne in mind that distention, per se, is a strong stimulus to glandular secretion so that in long-continued obstruction the distended portion of bowel is apt to pour out large quantities of fluid and salts which may be vomited or retained, if retained the secretion is excluded from the normal interchange of fluids and electrolytes and is just as effective a mechanism in producing the train of dehydration and electrolyte imbalance as if it had been vomited. The quantities of fluid so lost may be of unexpected magnitude. In the rabbit, which cannot vomit, intestinal obstruction may lead to the accumulation of as much as thirteen per cent of the animal's body weight in fluids found in the stomach and intestine postmortem. In the human being, during the course of untreated obstruction, analogous volumes of fluids and quantities of electrolytes are lost by the vomiting of gastric juice plus hepatic, pancreatic and intestinal secretions, depending upon the level at which obstruction has occurred.

The distention factor is, of course, well recognized today and the use of the Wangensteen apparatus or the Miller-Abbott tube has become a routine procedure in effecting decompression and evacuation of retained secretory products before or after appropriate surgical treatment. The relief of distention is thus accomplished efficiently but the very procedure leads to a great loss of fluids, salts and enzymes. In pyloric obstruction suction drainage of gastric contents may amount to over 6 liters a day⁴ and in itself provides a basis for the development of dehydration and dechlorination.

CHARACTERISTIC ALTERATIONS

In the majority of instances, these two factors—dechlorination and dehydration—are responsible for the chemical changes in intestinal obstruction. The characteristic alterations which result include

- 1 Hemoconcentration, with shrinkage of plasma volume
- 2 Reduction in the fixed base of the serum.
- 3 Diminution in plasma chlorides
- 4 Increase in blood urea and nonprotein nitrogen
- 5 Increasing carbon dioxide combining power of the plasma
- 6 Urine, often highly acid, which may contain ketone bodies, and shows a marked reduction in chloride content

Originally it was thought that the dehydration was simply the result of vomiting of quantities of digestive fluids, but according to Gamble and Ross⁴ the train of events begins with the loss of chlorides in the vomited material. As compared with blood plasma, gastric juice contains about 140 per cent of chloride, pancreatic secretion about 40 per cent, liver bile about 100 per cent and jejunal and ileal secretions about 125 per cent. Hence when large volumes of such fluids are lost, the withdrawal of chloride from the plasma and ultimately the tissues becomes a matter of great importance. In order to compensate for the hypochloremia, carbon dioxide is retained and bicarbonate increased so that the remaining chloride and the increased bicarbonate together may maintain a workable concentration of cations. However, if sufficient such retention of carbon dioxide and bicarbonate occurs, alkalosis develops and a renal mechanism comes into play by which increased quantities of sodium are excreted in the urine in an attempt to counter the alkalosis. This depletion of base, for which the body cannot compensate as it does for chloride, is accompanied by a proportionate water loss. The loss of electrolytes from the blood and tissues leads to dehydration of the tissues and hemoconcentration with reduction of the blood plasma volume.

Thus we arrive at the chemical factors of the most critical significance—dehydration and reduction of fixed base. The diminution of blood chlorides is probably due largely to their loss in gastric juice which is vomited or retained, but there may be additional factors such as a shift from blood to tissues or from plasma to corpuscles. Since the loss from vomiting is an obvious one, it has been widely held that the degree of hypochloremia largely depends upon the quantity of chloride secreted into the stomach. Under such circumstances it would be expected that in stenosing duodenal ulcer, when the gastric juice contains normal or excessive amounts of free hydrochloric acid, the extent of hypochloremia would greatly exceed that found in carcinomatous obstruction, where hypochlorhydria or achlorhydria most often exists. However, this does

not universally hold true and McVicar and Weir⁶ have stated that the concentration of free hydrochloric acid in the gastric juice cannot be correlated with the degree of hypochloremia present, citing instances in which it occurred in the presence of an acidity. Furthermore, it is difficult to correlate the levels of blood chloride with the clinical status of the patient in many instances. It is certain that the extent of plasma chloride diminution may be masked by the concomitant hemoconcentration so that it may not be a true index of chloride depletion.

In 1944 Coller⁷ and his associates concluded that the clinical status offered the best index for the administration of corrective measures. This impression has been borne out in the experience of the author with cases in which laboratory studies available at the time of need would have been misleading if not weighed against the observable clinical condition. In the case of a 36 year old male seen in 1945, vomiting from pyloric obstruction due to stenosing duodenal ulcer had led to moderately severe dehydration and prostration. Blood alkali studies were not then available—plasma chloride level was 590 mg per 100 cc (as NaCl), yet mild convulsive seizures, constant headache and dulled perception indicated the probability of alkalosis. Despite the administration of normal saline solution according to the simple rules of Power, Pederson and Maddock,⁸ the syndrome persisted while blood chloride levels remained within normal limits and hematocrit readings dropped from 61 to 47. In this instance, a quantity of saline solution approximately two and a half times the volume of fluid lost by vomiting per twenty-four hours was required for restoration of the clinically normal acid-base equilibrium.

In 1946, Sanchez-Vegas and Collins,⁹ investigating the electrolyte status of patients with pyloric obstruction due to duodenal ulcer, found marked diminution in urinary chlorides. This progressed to a point significantly below the normal 5 to 10 gm in twenty-four hours, as in the case cited above, even in the presence of normal plasma chlorides, but with marked alteration in the acid-base balance of the blood. In their opinion the decrease in urinary chlorides was due to depletion of the tissues in an attempt to maintain blood chloride content at or near a normal level. Whether we use the blood chloride level or the twenty-four hour excretion of urinary chloride as our measure of chloride loss, we must recognize that the organism attempts to compensate for its depletion by the retention of bicarbonate and may do so to the extent of developing alkalosis. It would be thought that the administration of normal saline solution with its replacement of water, sodium and chloride would invariably correct such an alkalosis, that is, if the patient were supplied with sufficient normal saline solution, and if ketosis were prevented, the electrolyte pattern of the plasma would be satisfactorily

adjusted by the kidneys. However, in some instances the excess sodium is not wholly excreted and the chloride administered may be incapable of displacing enough bicarbonate to nullify the alkalosis.

Zintel, Rhoads and Ravdin⁴ suggested in 1948 that ammonium chloride be used intravenously in a 2 per cent solution to supplement the other measure, and reported its successful use in seven patients. The solution is readily made up and sterilized by autoclaving for twenty minutes at 15 pounds pressure. The dosage is based on the patient's requirements, to reduce the carbon dioxide combining power by 1 per cent, ammonium chloride is given in the proportion of 16 mg per kilogram of body weight. No unfavorable reactions were encountered in this series. Since then this procedure has had fairly wide usage and very recently Grace and Barr¹⁰ described its application in nine cases of alkalosis, including two due to intestinal obstruction.

Grace and Barr also stressed two points of interest: first, the danger of inducing alkalosis by the administration of sodium lactate without the simultaneous use of normal saline while gastric suction is in operation, and second, the persistence of renal damage after continued alkalosis, at times to a point at which it appears to be permanent. On the other hand, in cases in which there is a greater loss of sodium than that of chloride, a status of acidosis may develop. This is particularly true when the loss of pancreatic, jejunal and ileal secretions is greater than that of gastric juice with its higher chloride content, and may be heightened by impairment of renal function. It is important to note at this point that where the acid base equilibrium is disturbed in either direction, this disturbance occurs simultaneously with dehydration and the primary corrective measure remains the same—the administration of water, sodium and chloride.

A state of ketosis may develop in the presence of either alkalosis or acidosis. We are accustomed to associating ketosis with acidosis due to starvation, as may well occur in intestinal obstruction. Abbott and Mellors¹¹ have demonstrated that in experimental low intestinal obstruction the late development of vomiting may permit evidence of starvation and malnutrition to long precede severe dehydration. At intermediate points of obstruction there may well be mixed states in which the development of starvation and the loss of chloride by vomiting occur at parallel rates. There it is possible that the excess of ketone acids due to starvation may yet be insufficient to balance the preponderance of accumulated bicarbonate which has resulted from chloride depletion. Again, however, regardless of the state of acidosis or alkalosis, correction of the ketosis lies in the administration of sufficient glucose to prevent the further incomplete breakdown of the even numbered fatty acids.

In addition to the foregoing, an increase in nonprotein nitrogen, first observed by Tileston and Comfort¹² in 1941, appears whenever complete gastrointestinal obstruction occurs at any level from the esophagus to the rectum. In comparison with most other types of azotemic retention, there is less effect on the urea nitrogen than on the remaining fractions, but both are increased. An increased destruction of protein due to the effects of starvation and dehydration upon tissue cells throughout the body has been repeatedly observed. Because of hemoconcentration and reduced blood pressure, the filtration pressure in the kidney is lowered and while the renal system may be able to concentrate well, it is usually unable to excrete the increased nitrogenous load so liberated, and hyperazotemia appears. As in the case of ketosis, the use of isotonic glucose solution tends to prevent the element of starvation in the destruction of protein and the administration of normal saline solution tends to restore the electrolytes, the loss of which is the major factor in the dehydration.

SUMMARY

To summarize, the physicochemical factors in gastrointestinal obstruction are based on the effects of distention and loss of fluid and electrolytes which lead to dechlorination, loss of fixed base and dehydration. This is evidenced in studies which show:

- 1 Hemoconcentration
- 2 Reduction in the fixed base of the serum
- 3 Diminution in plasma chlorides
- 4 Increase in urea and nonprotein nitrogen
- 5 Change in acid-base equilibrium, more often to alkalosis, not infrequently in the direction of acidosis
- 6 Hypochloremia and hypochloruria
- 7 Frequent ketosis and high acidity of the urine

These phenomena are readily countered in the majority of instances by the parenteral administration of adequate amounts of glucose and saline solutions. However, in some cases, ample quantities of these substances have been given to a point where the total serum base has been brought above the normal accepted range without controlling alkalosis. In these cases the intravenous use of 2 per cent ammonium chloride has been highly effective in treating or preventing the tetany, convulsions and possibly permanent renal damage which may result from alkalosis. The estimation of the quantities of fluids and electrolytes necessary to restore equilibrium is at present best made from serial studies of blood chlorides, carbon dioxide combining power, twenty-four hour urinary study for ketone bodies, urinary chloride excretion, intake and output records,

blood nonprotein nitrogen, all as adjuncts to the clinical observation of the patient.

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